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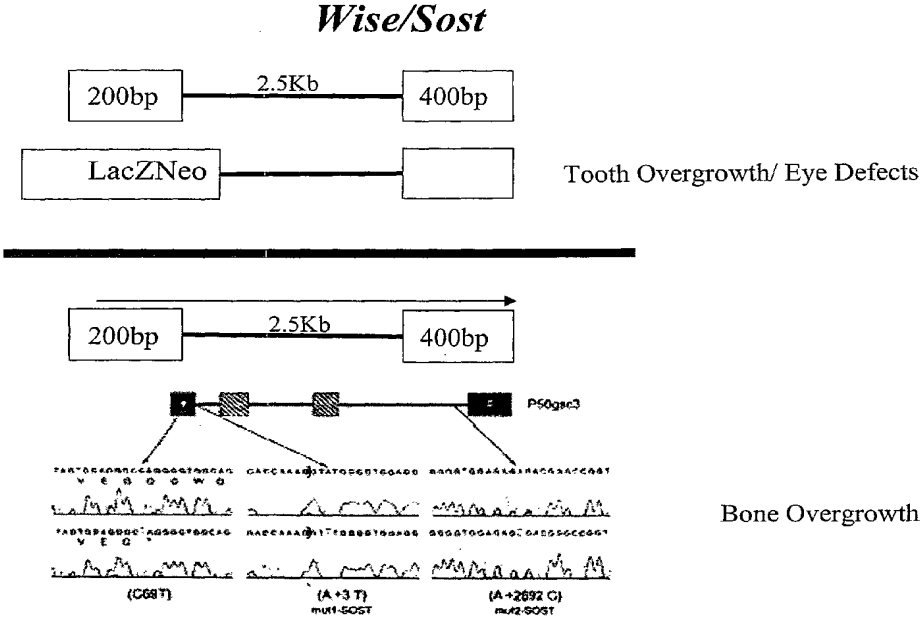
(54) Title: WISE/SOST NUCLEIC ACID SEQUENCES AND AMINO ACID SEQUENCES



(57) Abstract: The present invention relates to nucleic acid sequences and amino acid sequences which influence bone deposition, the Wnt pathway, ocular development, tooth development, and may bind to LRP. The nucleic acid sequence and polypeptides include Wise and Sost as well as a family of molecules which express a cysteine knot polypeptide. Additionally, the present invention relates to various molecular tools derived from the nucleic acids and polypeptides including vectors, transfected host cells, monochronal antibodies, Fab fragments, and methods for impacting the pathways.

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WISE/SOST NUCLEIC ACID SEQUENCES AND AMINO ACID SEQUENCES

This application is a non-provisional patent application based on U.S. Provisional Patent Application Serial No. 60/388,970, filed June 14, 2002, and a new U.S. non-provisional application based on Serial No. 60/388,970 filed June 16, 2003.

FIELD OF INVENTION

The present invention relates to Wise and Sost nucleic acid sequences and related amino acid sequences that can be used to influence bone deposition, the Wnt pathway, tooth development, and ocular development. In particular, the present invention also relates to nucleic acid sequences and amino acid sequences that optionally regulate or suppress bone deposition. The present invention relates to a family of nucleic acid molecules which expresses a family of amino acid sequences, some of which are characterized by a cysteine knot, such as the Wise and Sost proteins. The present invention also relates to resultant molecular biology tools derived from Wise or Sost, including plasmids, transfected host cells, antibodies, tranfected host organisms, and knockout organisms. Finally, the present invention relates to the interaction between Wise or Sost and LRP.

BACKGROUND OF INVENTION

To activate and study the Wnt pathway, a wide range of materials and information has been used. Various model organisms explained below are used because of differing developmental characteristics associated with the organisms. Because frogs and mice are exemplary of the organisms of study, they are explained in greater detail below. As will be seen,

frogs and mice were used in many of the Examples contained herein. Additionally, various genes and the Wnt pathway are explained.

Background of the Frog.

Frogs, in particular *Xenopus*, are excellent model organisms for testing embryonic development. Two species of *Xenopus* are commonly used for testing, *Xenopus laevis* and *Xenopus tropicalis*. Both *Xenopus* species are natives of Africa. *Xenopus laevis* has been used for many years to investigate the early period of embryonic development. Embryos develop rapidly after fertilization, and a tadpole with a fully functional set of organs forms within a couple of days. Thus, experiments can be conducted on the embryos directly following fertilization. The embryos can develop in a simple saline solution over a few days. The tadpoles are then examined to determine if the experimental intervention had any observable effect. The role of genes in development can be assayed by injecting a tiny amount of any messenger RNA (mRNA) encoding the gene of interest into an early embryo, then once again allowing the embryo to grow into a tadpole.

The *Xenopus* embryo has long served as a major model for the study of embryonic development because of its numerous advantages, including external development, large size, identifiable blastomeres, and its ability to withstand extensive surgical intervention and culture *in vitro*. These advantages enable extensive investigation of the earliest embryonic patterning events. In fact, much of the current understanding of early embryonic development derives from experiments performed in the *Xenopus* embryo.

More particular to the frog, the earliest events of all animal embryos are controlled by mRNAs that are deposited in the egg by the mother. These maternal mRNAs control the embryonic processes that occur prior to the transcription of the embryonic genome. These

processes can best be examined in *Xenopus* because, in these embryos, they occur during an especially long period of time, and because they occur while the embryo is developing externally. Such features have resulted in a detailed cellular and molecular understanding of early patterning events, including a comprehensive view of the role of specific extracellular growth factors, cell surface receptors, and intracellular signaling pathway components. These events include the patterning of the basic body plan, the determination of cell fate, and the early patterning of major organs, including the digestive system, circulatory system, and nervous system. In addition, many of the factors originally identified in *Xenopus* have been subsequently shown to control numerous later developmental events, as well as other critical biological processes, and oncogenesis. Finally, *Xenopus* is a major contributor to understanding cell biological and biochemical processes, including chromosome replication; chromatin, cytoskeleton, and nuclear assembly; cell cycle progression; and, intracellular signaling. Thus, *Xenopus* is ideally suited for studying early embryonic patterning and cell fate determination, later development, and organogenesis, oncogenesis, and cell biological and biochemical processes.

Background of A-P Patterning.

The mechanisms that generate regional differences along the anterior posterior (A-P) axis of the vertebrate nervous system play an important role in pattern formation during development. The classical activation/transformation model proposed by Nieuwkoop suggests that an initial signal induces neural tissue of anterior type and then a second transforming signal differentially acts on it to convert cells to a more posterior character (Nieuwkoop, 1952; Slack and Tannahill, 1992). This transformer or "posteriorizing factor(s)" thus modifies a ground state to generate the full spectrum of neural structures along the A-P axis. However, patterning of the anterior region

is clearly more complicated than a simple default state of neural induction. This is highlighted by the presence of local inductive centers, such as the anterior visceral endoderm and the isthmus, which are essential for anterior neural development. Hence, models for a coordinated mechanism of A-P patterning in the nervous system need to integrate the influence of local signals on rostral brain patterning, with the influence of posteriorizing factors that work more generally on the hindbrain and spinal cord.

Analysis of posteriorizing signals in neural patterning is complicated by the tissue interactions and dynamic morphogenetic movements which occur during gastrulation. *Xenopus* animal caps provide a simplified system for studying patterning events separately from morphogenetic movements. Animal caps alone form epidermis in culture, but when treated with antagonists of Bone Morphogenic Protein (BMP) signaling, such as Noggin, Chordin, Follistatin, or truncated BMP receptors, they adopt an anterior neural fate. Using these molecules as neural inducers, experimental studies in animal caps have provided evidence that fibroblast growth factor (FGF), retinoic acid (RA), and Wnt (Wingless and iNT-1) signaling pathways influence A-P patterning by inducing posterior characters. Wnt is also known as the canonical Wnt pathway and the Wnt planar polarity pathway. Thus, *Xenopus* embryo assays and experiments in other vertebrates provide more evidence that RA, FGF, and Wnt pathways influence A-P patterning. It is desired to better understand the relative roles of these biochemical cascades, the degree to which they are used at any particular axial level, and how they are integrated in organizing normal A-P patterning.

Mesoderm plays an important early role in A-P patterning of neural tissue. Mesoderm is the middle layer of embryonic cells between the ectoderm and endoderm in triploblastic animals, and forms muscle, connective tissue, blood, lymphoid tissue, the linings of all the body cavities,

the serosa of the viscera, the mesenteries, and the epithelia of the blood vessels, lymphatics, kidney, ureter, gonads, genital ducts, and suprarenal cortex. Experiments in *Xenopus* have shown that planar signals within the neuroectoderm and vertical signals from the underlying mesoderm work in concert to control regional identity of the nervous system. While early A-P specification of the nervous system occurs during gastrulation, it is not irreversibly committed to a particular identity. Grafting experiments in several species reveal plasticity in regional character and show that mesoderm is still playing a role at later stages. For example, analysis of the Hoxb4 gene has shown that its expression pattern is established through interactive signaling between the neural tube and the surrounding mesoderm. Furthermore, somites and paraxial mesoderm are sufficient to re-program Hox expression in the neural tube to a more posterior character when grafted ectopically. The ability of mesoderm to regulate regional character from early gastrula stages and to program motor neuron sub-type identities further emphasizes the importance of mesoderm and its signaling in patterning the developing nervous system.

The study of A-P patterning and focus on the mesoderm is of particular importance in the present invention because such patterning impacts bone development in an embryo. Pathways which control A-P patterning often impact bone development.

As such, it is desired to better understand the process of posteriorization. The identification of new factors that can modulate existing pathways, such as Wnts, FGF, and RA, or which represent novel signaling inputs will be beneficial to understanding how A-P patterning is coordinated. In particular, it is desired to understand how the Wnt pathway is activated and controlled. *Xenopus* has been used to study A-P patterning, that, in turn, is apparently impacted by the Wnt pathway. *Xenopus* can also be used to study activators or inhibitors of the Wnt pathway.

Background of Mouse Model.

Mice are also excellent model organisms for testing embryonic development. Mice and humans possess similar genes, mice show many clinical symptoms of human disease, and powerful techniques are available for genetic alterations of the mouse genome. All of these factors make mice excellent experimental models for testing new therapies. Mice share many fundamental biological processes with humans therefore, mice are considered to be one of the most significant laboratory models for human disease and genetic mutations. Research regarding human biological processes and genetic diseases can be greatly enhanced by studying the mouse model for similar biological processes and diseases.

Mice have been a preferred experimental model for a number of years due to their small size, short life span, and the female's ability to produce a litter within two months after her birth. These factors allow researchers to follow a given disease process from beginning to end within a short time frame. For these various reasons, mouse models are preferred for testing new drug therapies, designing novel therapies, and studying genetic diseases potentially also affecting humans.

Genes can be inserted into a fertilized mouse egg by several methods including physical injection. The gene is first attached to a promoter and then is injected into the fertilized egg. The fertilized egg is implanted into a female mouse and the embryo is allowed to develop to a specified given stage for study. Once embryos reach the desired stage of development, they can be harvested and tested to determine experimental results. Alternatively, embryos can be allowed to develop into full-term pups prior to being harvested to determine the results of the experiment.

Because mice are phylogenetically closely related to humans with regards to biological processes and diseases, and because of the rapidity of mouse embryological development, they are considered to be an excellent animal model for the study of human development, biological processes, and disease.

Background of Wnt.

Wnt proteins form a family of highly conserved secreted signaling molecules that regulate cell-to-cell interactions during embryogenesis. Wnt genes and Wnt signaling are also implicated in aberrant cancer cell regulation. Insights into the mechanisms of Wnt action have emerged from several systems: genetics in *Drosophila* and *Caenorhabditis elegans* (*C. elegans*); and, biochemistry in cell culture and ectopic gene expression in *Xenopus* embryos. Many Wnt genes in the mouse have been mutated, leading to very specific developmental defects. As currently understood, Wnt proteins bind to receptors of the Frizzled family on the cell surface. Through several cytoplasmic relay components, the signal is transduced to β-catenin, which then enters the nucleus and forms a complex with TCF or LEF to activate transcription of Wnt target genes. The extracellular Wnt ligand binds the transmembrane receptor Frizzled (Fz), which activates the cytoplasmic phosphoprotein Dishevelled (Dsh). Activated Dsh inhibits GSK3 β-mediated degradation of β-catenin. β-catenin protein, therefore, accumulates and, in association with transcription factors (TCF-3, TCF-4, LEF), regulates gene transcription in the cell nucleus.

Wnt-proteins, secreted glycoproteins, serve as important signaling molecules during development of invertebrates and vertebrates. They have been shown to play crucial roles in such diverse processes as cancer, organogenesis, and pattern formation. To date, 19 Wnt genes have been isolated in higher vertebrates, 7 have been found in the genome of *Drosophila*, and 5 in the *C. elegans* genome. Wnt genes are defined by their sequence similarity to the founding

members, Wnt-1 in the mouse (originally called iNT-1) and wingless (Wg) in *Drosophila*. The genetic analysis of the Wg signaling pathway in *Drosophila* has led to the identification of many downstream components, which have been shown to be functionally conserved in other organisms. Wg/Wnt-proteins are thought to signal through seven-transmembrane receptors encoded by the Frizzled (Fz) gene family to regulate the stability of an effector protein known as armadillo (Arm) in flies or β-catenin (β-cat) in vertebrates, which eventually leads to the activation of target genes through a complex of Arm/β-cat, with DNA-binding transcription factors of the TCF/LEF family. This pathway is referred to as the canonical Wnt-pathway.

In recent years, evidence has been provided that Wnt signaling in the chick is involved in a variety of processes associated with skeletogenesis, such as chondrogenesis and joint development. Previously, it has been shown that there are at least three Wnt genes, Wnt-4, Wnt-5a, and Wnt-5b, as well as components of the canonical Wnt signaling pathway, expressed in chondrogenic regions, and that there is a fourth Wnt gene, Wnt-14, which is expressed early in the joint forming region (Fig. 1D). Wnt-4 is also expressed in regions of the joint, however, its expression is restricted to cells in the periphery of the joint interzone (Fig. 1C). Wnt-5a expression is restricted to cells in a region of the perichondrium which will develop into the periosteum (Fig. 1A), while the closely related Wnt-5b gene is expressed in a sub-population of prehypertrophic chondrocytes, as well as cells of the outer layer of the perichondrium (Fig. 1B).

Much of what is known about the functional role of Wnt signaling in early vertebrate development comes from experiments with *Xenopus*. Maternally encoded components of the canonical Wnt signaling pathway function to establish the endogenous dorsal axis. The sperm fertilizing the egg triggers cortical rotation. Vesicles are moved towards the future dorsal side. A dorsal determinant, which is likely to be Dishevelled, is transported with these vesicles.

Dishevelled accumulates on the dorsal side and inhibits GSK3. β-catenin can therefore accumulate on the dorsal side and, together with XTCF-3, induce the expression of siamois, which regulates down-stream dorsal development.

As such, the Wnt signaling system is one of only a limited number of signaling systems used during embryonic development to pattern the ultimate resultant morphological physical body construction plan. Clearly, Wnt signaling is triggered at several discrete time points during development, both at different developmental stages and within different tissues (*see* Table below).

TABLE 1

Gene	Expression	Function
XWnt-1	anterior neural	mid-/hindbrain boundary
XWnt-2 (=XWnt-2B)	neural and heart	not known
XWnt-3-A	posterior neural	neural anteroposterior patterning
XWnt-4	neural, kidney (pronephros)	kidney morphogenesis
XWnt-5A	ectoderm	not known
XWnt-8	ventral mesoderm	mesodermal patterning
XWnt-8b	forebrain	not known
XWnt-11	dorsal marginal zone	gastrulation movements

Early *Xenopus* development provides an excellent model system for studying the general questions of tissue-specific response to Wnt signaling. Before the onset of zygotic transcription at the Mid-Blastula Transition (MBT) phase, the Wnt pathway functions to establish the dorsal body axis. Only an hour or two later, after MBT, XWnt-8 functions to promote ventral and lateral mesoderm. These strict stage-specific responses to Wnt signaling could conceivably be induced by differential use of the canonical and alternative Wnt signal transduction pathways.

It is further known to those of skill in the art that Wnt genes are active in osteoblast cells. Wnt regulates bone deposition in embryos and in mature individuals. It has been found that Wnt signals impact the dorsal-ventral pattern in early *Xenopus* embryo. In late embryos, Wnt causes

anterior-posterior patterning of the neural tissue, neural crest formation, and organogenesis. As such, it is desired to have compositions and methods for controlling Wnt signaling. Such compositions and methods would have impact on embryonic developmental processes such as anterior-posterior patterning and on bone deposition.

Background of Sost.

Sost is believed to be a Bone Morphogenic Protein (BMP) antagonist. Mutations in the human Sost gene on human chromosome 17 can result in sclerosteosis, which is an autosomal recessive sclerosing bone dysplasia characterized by progressive skeletal overgrowth. A high incidence of the bone dysplasia disorder, occurring as a result of a founder effect in affected individuals has been reported in the Afrikaner population of South Africa, where a majority of individuals are affected by the disorder. Homozygosity mapping in Afrikaner families, along with analysis of historical recombinants, localized sclerosteosis to an interval of ~ 2 cm. between the loci D17S1787 and D17S930 on chromosome 17q12-q21. Affected Afrikaners carry a nonsense mutation near the amino terminus of the encoded protein, whereas an unrelated affected person of Senegalese origin carries a splicing mutation within the single intron of the gene. The Sost gene encodes a protein that shares structural and functional similarity with a class of cysteine knot-containing factors, including dan, cerberus, gremlin, and caronte. The specific and progressive effect on bone formation observed in individuals affected with sclerosteosis suggests that the Sost gene encodes a regulator of bone homeostasis.

As such, evidence is provided herein that the deficiency of the Sost gene product, a novel secreted protein expressed in osteoblasts, leads to the increased bone density in sclerosteosis. The two nonsense mutations, and the splice site mutation, are loss-of-function mutations. Previously, the precise function and working of Sost was believed unknown, an inhibitory effect

on bone formation can be proposed since pathophysiological analysis indicated that sclerosteosis is primarily a disorder of increased formation of normal bone. While it is known that Sost impacts bone formation, it is desired herein to better delineate the mechanism of action and pathway of Sost's bone deposition activity. Previously, it has been hypothesized that Sost affected BMP rather than the Wnt pathway. Previous to our described invention herein, it was not known that Sost reacted with Wnt pathway elements. The Sost-Wnt pathway interaction can be alternatively direct or indirect in nature.

Background of LRP6.

LRP genes encode the low-density lipoprotein (LDL)-receptor-related proteins, LRP5 and LRP6. Human LRP5 and LRP6 share 71% amino-acid identity, and together with Arrow, form a distinct subgroup of the LRP family. Arrow, LRP5, and LRP6 each contain an extracellular domain with epidermal growth factor (EGF) repeats and low-density lipoprotein receptor (LDLR) repeats, followed by a transmembrane region and a cytoplasmic domain lacking recognizable catalytic motifs. An LRP6 mutation in mice results in pleiotropic defects recapitulating some, but not all, of the Wnt mutant phenotype. LRP5/LRP6 involvement in Wnt signaling and LRP function in Wnt-induced axis *Xenopus* embryos have been previously studied.

LRPs and Arrow in *Drosophila* are long single-pass transmembrane proteins. These proteins are of interest because they interact with and affect Wnt signaling. Arrow is genetically required for Wingless (Wg) signaling (Wehril, 2000) and mouse LRP mutations are similar in phenotype to Wnt mutants (Pinson, 2000). In *Xenopus*, over-expression of LRP can activate Wnt signaling (Tamai, 2000). There is evidence that Wnts can bind directly to the extra-cellular domain of LRP and form a ternary complex with the Frizzled receptor (Tamai, 2000). Also, the

cytoplasmic domain of LRP can interact with Axin (Mao, 2001). Thus, LRP/Arrow appear to be important to understanding Wnt.

As stated, the Frizzled (Fz) family of serpentine receptors function as Wnt receptors, but how Fz proteins transduce signaling is not understood. In *Drosophila*, Arrow phenocopies the Wingless (DWnt-1) phenotype, and encodes a transmembrane protein that is homologous to two members of the mammalian low-density lipoprotein receptor (LDLR)-related protein (LRP) family, LRP5 and LRP6. It is reported that LRP6 functions as a co-receptor for Wnt signal transduction. In *Xenopus* embryos, LRP6 activated Wnt-Fz signaling, and induced Wnt responsive genes, dorsal axis duplication, and neural crest formation. An LRP6 mutant lacking the carboxyl intracellular domain blocked signaling by Wnt or Wnt-Fz, but not by Dishevelled or β-catenin, and inhibited neural crest development. The extracellular domain of LRP6 bound Wnt-1 and associated with Fz in a Wnt-dependent manner. This indicates that LRP6 is likely to be a component of the Wnt receptor complex.

Further, Wnt/β-catenin signaling induces dorsal axis formation through activation of immediate, early responsive genes, including nodal-related 3 (Xnr3) and Siamois (Sia). It has been shown that in two developmental processes dependent on the Wnt pathway in *Xenopus* -- secondary axis and neural crest formation -- LRP6 activates, but a dominant-negative LRP6 inhibits, Wnt signaling, providing compelling evidence that LRP6 is critical in Wnt signal transduction. LRP6 functions upstream of Dsh in Wnt-responding cells, synergizes with either Wnt or Fz, and importantly, is able to bind Wnt-1 and to associate with Fz in a Wnt-dependent manner. The simplest interpretation of these findings is that LRP6 is a component of the Wnt-Fz receptor complex.

Genetic studies of Arrow in *Drosophila* and LRP6 in mice strongly support this hypothesis. Data also indicates the possibility that Wnt-induced formation of the Fz-LRP6 complex assembles LRP6, Fz and their associated proteins, thereby initiating cytoplasmic signaling. Consistent with this notion, Wnt signal transduction requires intracellular regions of both Fz and LRP6, which harbor candidate protein-protein interaction motifs. Notably, Arrow does not exhibit Fz planar polarity phenotype, implying that Arrow-LRP6 may specify Wnt-Fz signaling towards the β-catenin pathway. How Fz, LRP6, and proteoglycan molecules, such as Dally, interact to mediate Wnt recognition/specificity, and signal transduction remains to be elucidated. Thus, it is understood that LRP interacts with Wnt. The present invention is designed and characterized to control LRP binding to Wnt and Fz, and, more particularly, to control LRP upstream.

Background of LRP5.

In humans, low peak bone mass is a recognized significant risk factor for osteoporosis. It has been reported that LRP5, encoding the LDLR-related protein 5, affects bone mass accrual during growth. Mutations in LRP5 cause the autosomal recessive disorder osteoporosis-pseudoglioma syndrome (OPPG). OPPG is an autosomal recessive disease, characterized by severe osteoporosis due to decreased bone formation and pseudoglioma resulting from failed regression of primary vitreal vasculature. Y. Gong, et al. (2001). Gain of gene function leads to high bone mass (HBM) phenotype as an autosomal dominant trait, whereas loss of function leads to osteoporosis.

It has been found that OPPG carriers have reduced bone mass when compared to age- and gender-matched controls. LRP5 expression by osteoblasts *in situ* has been demonstrated and LRP-5 has been shown to reduce bone thickness in mouse calvarial explant cultures. These data

indicate that Wnt-mediated signaling via LRP5 affects bone accrual during growth and is important for the establishment of peak bone mass.

In mice, it has been found that LRP5 participates in bone formation and bone mass. Null mutation of LRP5 causes post-natal bone loss, resulting from decreased bone formation and osteoblast proliferation, independent of Runx2. M. Kato, et al. (2002). In contrast, transgenic mice expressing LRP5 with the HBM mutation G171V exhibit increased bone formation and bone mass, without skeletal developmental abnormalities. F. Bex, et al. (2002).

LRP5 appears to interact with the Wnt pathway since LRP5 with the HBM mutation prevents inhibition of Wnt signaling by Dikkopf-1. L. M. Boyden (2002); A. M. Zorn (2001). There is murine hybridization and microarray evidence that indicates Wnt signaling is involved in bone fracture repair. M. Hadjiargyrou (2002). Six additional mutations in LRP5, located in the amino-terminal domain near G171, have been identified. These mutations cause increased bone density, particularly in cortical bone. L. Van Wesenbeeck (2003).

Background of β-catenin.

β-catenin reports demonstrate its accumulation opposite the sperm entry point by the end of the first cell cycle. β-catenin continues to accumulate in dorsal (*i.e.*, opposite the sperm entry point) but not ventral cytoplasm through the early cleavage stages. By the 16- to 32-cell stages, it accumulates in dorsal but not ventral nuclei. Remarkably, the pattern of dorsal accumulation of β-catenin closely parallels the ability of transplanted dorsal cells to induce an axis when implanted into host embryos. Thus, β-catenin is the first signaling molecule to show a dorso-ventral polarity in the early embryo. Combined with the loss-of-function data from Heasman et al., it is now clear that when fertilization elicits a cortical rotation, and displacement of material

and organelles to the future dorsal side, it leads to a dorso-ventral asymmetry in β-catenin, which is required for axis formation.

Brannon et al. show that the HMG Box factor XTCF-3 directly binds the siamois promoter. In the absence of β-catenin, XTCF-3 inhibits gene expression. However, on the dorsal side of the embryo, β-catenin binds the XTCF-3, and, thus, activates the gene. This is notable because siamois is a homeobox gene likely playing a major role in specifying formation of Spemann's Organizer. Therefore, a dorso-ventral difference in β-catenin forms within an hour or two of fertilization, directly regulating a key homeobox gene in the blastula, thus contributing to formation of Spemann's Organizer on the dorsal side of the gastrula.

β-catenin not only impacts development, but it influences bone development in adults. Regulation of osteoblasts results from accumulation of β-catenin in the cell. It is desired to have methods and compositions for controlling bone deposition. It is known that the Wnt pathway controls accumulation of β-catenin, which regulates osteoblast expression. It is desired to control and inhibit osteoblast regulation by preventing Wnt pathway activation. For this reason, the present invention includes nucleic acid molecules and amino acid sequences for controlling Wnt.

SUMMARY OF INVENTION

The present invention relates to Wise nucleic acid sequences and amino acid sequences, Sost nucleic acid sequences and amino acid sequences, and LRP nucleic acid sequences and amino acid sequences. Additionally, the present invention relates to control over the influencing of bone deposition, ocular development, tooth development, and the Wnt pathway using the above nucleic acid sequences and amino sequences. Additionally, the present invention relates to molecular tools developed from the nucleic acids and polypeptides including

vectors, transfected host cells, transfected organisms, knockout organisms, antibodies, hybridomas cells, Fab fragments, and homologous nucleic acid sequences and polypeptides. Mutants of the Wise, Sost, and LRP nucleic acid sequences and polypeptides are contemplated herein and are used to influence the pathways. The Wise and Sost nucleic acid sequences are generally about 70% homologous. Related to this are cysteine knot polypeptides which bind to LRPs as well as a variety of polypeptides. There is a family of nucleic acid sequences and polypeptides expressed therefrom, which are related to the Wise and Sost sequences. The host cells that can be treated with the mutants of the present invention include insects, amphibian, and mammalian cells.

Nucleic acid sequences, and the resultant polypeptides, are members of a family of isolated nucleic acid molecules which influence one of the following: tooth development, Wnt pathway activation, bone deposition, or ocular development is contemplated herein. The family includes a variety of nucleic acid molecules including NDP, DAN, Caronte, PDGF, Wise, Sost, Cereberus, Gremlin, CTGF, Soggy, DKK1, Cyr61, DKK2, DKK3, DKK4, NOV, Mucin, Slit, OOH, Wisp, and CCN. Related to this are the LRP family of molecules which also influence these various pathways. In particular, LRP 1, 2, 5, and 6. As such, the family that expresses a cysteine knot polypeptide binds to one of the LRPs. The various nucleic acids are specifically listed in the Sequence ID listing included herewith. Related to this are degenerate variants of the nucleic acid molecules. As mentioned, the family of nucleic acid molecules typically expresses a polypeptide that includes a cysteine knot protein, with the cysteine knot protein including eight cysteine residues. However, variations of the cysteine knot protein are available for use. As such, any nucleic acid sequence which impacts the previously mentioned pathways and expresses a cysteine knot protein is believed related to the present family of

nucleic acid sequences. It is known that Exon 2 of the Wise nucleic acid sequence (SEQ. ID. NO. 128) expresses a desired cysteine knot protein. As such, oligonucleotide fragments which are 70% homologous to Wise Exon 2 are believed to be potentially related to the present family of nucleic acid molecules.

Mutant versions of the above nucleic acid molecules can result in increased bone deposition, as well as tooth development and ocular development. Additionally, the mutants will influence with Wnt pathway activation. As such, mutant versions of the nucleic acid molecules of the present invention are known to impact the mentioned pathways in a variety of ways. The present invention resultingly relates to any mutant version of the listed nucleic acid sequences. The mutants can be generated via point, frame shift, deletion, or loss of function mutations. Loss of function mutations can be achieved by placing a stop codon near the beginning of the selected nucleic acid sequences, which would include before or after the start of the sequence. For example, a stop codon can be placed just after the start of Exon 1 of the Wise nucleic acid sequence. During translation the stop codon will prevent translation of the Wise Exons and therefore the polypeptide will not be expressed. Other available mutants include antisense RNAs, morpholinos, antisense oligonucleotides, mRNAs translated from the selected nucleic acid sequences, and RNAi complementary to the nucleic acids sequences.

As discussed herein, nucleic acid sequences and nucleic acid molecules will be used interchangeably. The isolated nucleic acid sequences include gDNAs, cDNAs, and a variety of other nucleic acid sequence fragments. It is contemplated that any of a variety of nucleic acid sequences can be used herein including genes, mRNA, cDNA, gDNA, tRNA, oligonucleotides, polynucleotides, and nucleic acid sequence fragments. As such, any nucleic acid sequence which expresses a polypeptide that influences either tooth development, Wnt

pathway activation, bone deposition, or ocular development is contemplated as part of the present invention, as well as mutant versions thereof. The nucleic acid sequences will include genes which are any hereditary unit that has an affect on the phenotype of an organism and can be transcribed into mRNAs which result in polypeptides, as well as rRNAs or tRNA molecules and regulatory genes. Also, alleles and mutant alleles are part of the definition of a gene as used herein.

Probes which hybridize to either mutant nucleic acid sequences or the non-mutant nucleic acid sequences are part of the present invention. The probes will include any of a variety of labels and can be either cDNA or RNA probes. The probes can be used to form a kit or similar tool for use in detecting the presence or absence of a particular Wise, Sost, or LRP nucleic acid or polypeptide.

Vectors are formed from both the isolated nucleic acid sequences and the mutant versions of the isolated nucleic acid sequences. The vectors include expression, cloning, and viral vectors. Other available vectors include fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-hybrid vectors, sequencing vectors, and cloning vectors. Also, prokaryotic and eukaryotic vectors may be used. Specific prokaryotic vectors that may be used in the present invention include pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280, pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT. Specific eukaryotic vectors that may be used herein include pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo, pSVK3, pSVL, pMSG, pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis. As mentioned, a variety of promoters may be used

with the vector, as well as any of a variety of selectable markers. Available markers include antibiotic resistance genes, a tRNA gene, auxotrophic genes, toxic genes, phenotypic markers, colorimetric markers, antisence oligonucleotides, restriction endonuclease, enzyme cleavage sites, protein binding sites, and immunoglobulin binding sites. Specific selectable markers available include LacZ, neo, Fc, DIG, Myc, and FLAG.

Any of a variety of host cells, including prokaryotic and eukaryotic cells, can be transfected with the vectors previously mentioned. Prokaryotic host cells include Gram-negative and Gram-positive bacteriums may be transfected with any of the variety of the vectors previously mentioned. Available bacteriums include Escherichia, Salmonella, Proteus, Clostridium, Klebsiella, Bacillus, Streptomyces, and Pseudomonas. A preferred Gram-negative bacterium is Escherichia coli. Eukaryotic vectors can be used to transfect eukaryotic host cells including yeast, plant, fish, mammalian, human, mouse, frog, or insect cells. Specific host cells that can be transfected include ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, chrondocytes, and human or mammalian bone marrow stroma. As such, the present invention includes host cells transfected with any of the previously mentioned vectors.

It is specifically contemplated that mutant Wise nucleic acid sequences can be used. The mutant Wise nucleic acid sequences will be mutated versions of SEQ. ID. NO. 1-5, 126-128, 109, 96, and 97, as well as complementary mutant sequences thereof. Additionally, degenerate variants of these sequences may also be used. Plasmids can be formed from these mutant Wise nucleic acid sequences, as well as transfected host cells. Additionally, mutant organisms can be formed from the mutant Wise nucleic acid sequences, including Wise mutant mice. Sost and LRP can also be mutantized and various related constructs can be formed

therefrom. Specific mutants to either Wise, Sost, or LRP can be developed related to SEQ. ID. NO. 1-44, 96-103, 108, 110-113 and 126-128 listed herein.

Amino acid sequences which influence at least one of the following, tooth development, Wnt pathway activation, bone deposition, or ocular development are part of the present invention. Available amino acid sequences include those polypeptides or proteins expressed from the previously discussed nucleic acid molecules. In particular, Wise, Sost, and LRP polypeptides and amino acid sequences can be used herewith. Specifically available amino acid sequences include those listed in the SEQ. ID. NO. 45-95, 104-107, 109, 114-125. Isolated polypeptides that have a cysteine knot formed from eight cysteine knot residues which impact the previously listed pathways are included herewith. Finally, amino acid sequences which are 70% homologous to Exon 2 polypeptides of Wise may be used herewith. When used herein amino acid sequences include any of a variety of polypeptide and protein molecules.

Antibodies which bind to at least one of the previously mentioned amino acid sequences are used herewith. The antibodies include monoclonal, polyclonal, recombinant, and antibody fragments. Any of a variety of antibodies may be used that bind to either Wise, Sost, or LRP 1, 2, 5, or 6. The antibodies are designed to either bind to the selected polypeptide and prevent it from binding to its normal antigen. Conversely, the antibodies can be designed such that they attack and destroy the chosen or selected polypeptides. For example, it is preferred to bind either Wise or Sost with Wise or Sost antibody, respectively, whereby Wise or Sost is prevented from binding to LRP 5 or 6. As such, it is desired to have antibodies that specifically bind Wise, Sost, or LRP. Related to the antibodies are Fab fragments which function the same way as the chosen antibodies. These anti-peptide antibodies will prevent binding by the selected amino acid sequence to an LRP for example. The antibodies can be directed to both mutant and

non-mutant versions of polypeptides expressed from the mutant or non-mutant versions of the nucleic acid sequences.

Hybridomas can be formed which are used to produce the desired antibodies. As such any of a variety of cells can be used to produce both the polypeptides as well as the antibodies.

It is known that both Wise and Sost polypeptides bind to LRP 5 or 6 polypeptides. As such, the present invention relates to a protein molecule formed from a Wise polypeptide bound to an LRP polypeptide. Additionally, the present invention relates to a Sost polypeptide bound to an LRP polypeptide.

Use of the isolated nucleic acid sequences or polypeptides can specifically result in increased bone deposition, both *in vivo* and *in vitro*. As such a variety of methods can be practiced which are designed to increase the bone deposition either in a selected cell or a selected host organism. One particular method includes isolating a nucleic acid sequence which can be either Wise, Sost, or LRP. The nucleic acid sequence then is used to form a cassette which includes a stop codon at the beginning of the nucleic acid sequence. Preferably, the cassette will include a marker and a promoter. The selected nucleic acid sequence can be either a mutant or a non-mutant nucleic acid sequence, with the sequence selected dependent upon the desired outcome. The cassette is then used to form a plasmid whereby any of a variety of plasmids, as previously mentioned, may be used. Once the plasmid is formed it is used to transfect a host cell. Any of a variety of methods can be used to transfect a host cell including microinjection. The available host cell will include a variety of prokaryotic and eukaryotic cells. Among the available cells are embryonic stem cells, blastomeres, and a variety of other stem cells. Once the host cell is transfected the stop codon can be activated to cause a loss of function mutation which

results in a phenotypic change. Among the phenotypic changes are increased bone deposition. The transfected host cells can also be used to transfect a host cell organism such as a mouse. The cells are injected into an embryo with the embryo then allowed to develop or mature. Host cells include insect, amphibian, and non-human mammal. Human cells can also be treated *in vitro*. Specific delivery of the nucleic acid sequence into the host cell can be accomplished via microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation. Desired host cells include osteoblasts, osteoclasts, and chrondocytes. Besides attaching stop codons to the nucleic acid sequence in the plasmid, other mutantized versions may be used. In particular, an alternative to the stop codon are point mutations, frame shift mutations, and other mutations may be used to preclude accurate translation of the polypeptide. This will resultingly achieve the same effect as a loss of function mutation. In particular, antisense RNA vectors may be used in the alternative.

Bone deposition can also be increased as an alternative method. A nucleic acid sequence can be selected, including Wise, Sost, or LRP. A nucleic acid sequence is then used to form a plasmid vector whereby the vector is used to transfect the host cell. The host cell will express the nucleic acid sequence to produce a polypeptide. Once a sufficient amount of polypeptide is produced it can be harvested for use in immunizing a host organism. Available host organisms include mice, rats, goats, rabbits, and any of a variety of other organisms used to produce polypeptides. The immunized host organism will produce antibodies to the polypeptide that was used to immunize the host.. After a period of time the antibodies may be isolated and separated from the host. The antibodies can be used as is or can be further treated to produce Fab fragments or related small molecules. Regardless of the selected form of the antibody it can be combined with a carrier. Any of a variety of carriers are available for use including liposomes.

The carrier antibody combination is used to transfect a host cell. This can be done either *in vitro* or *in vivo*. The antibody will bind to the selected target polypeptide and prevent activation of a selected pathway. This process can also be used in association with the Wnt pathway, tooth development or ocular development.

Any of a variety of kits may be formed both to the polypeptides or the nucleic acid sequences of the previously mentioned constituents. The kits can be used to detect the presence of a particular nucleic acid sequence or polypeptide or the absence of such composition.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the isolation of Wise by *Xenopus* animal cap screening;

Fig. 1A shows an illustration of the screening procedure;

Fig. 1B shows the RT-PCR gel electrophoresis results of the first round of screening;

Fig. 1C shows the RT-PCR analysis of injections using RNA from the isolated Wise clone;

Fig. 2 shows Wise as a conserved secreted protein;

Fig. 2A shows the alignment of the predicted amino acid sequence of Zebrafish, *Xenopus*, chick, mouse, and human Wise proteins. Shaded boxes represent identical amino acids between species; asterisks indicate residues conserved in *Drosophila* Slit, and dots identify residues conserved in Cef10. Circles mark conserved cysteine residues. The arrowhead delineates the site of signal peptide cleavage predicted in the chick clone;

Fig. 2B is a diagram showing alignment of conserved amino acids between Wise, Slit, and Cef10 (a CCN family member). Filled ovals and red lines indicate cysteine residues in the Slit homology domain conserved in the CT domain of CCN family members but not in Wise or

Slit. Dotted lines show other conserved amino acids. Shaded boxes in Wise indicate three blocks Δ1, Δ2, Δ3 deleted separately for functional analysis;

Fig. 2C shows Western blot detecting HA-tagged Wise protein secreted into the medium following RNA injection into oocytes and control uninjected oocytes;

Figs. 2D and 2E show the recombination between Noggin-expressing and Wise-expressing animal caps assayed for expression of Krox 20 (Fig. 2D) or en2 (Fig. 2E). Wise induces a ring of En2 (en) expression or patches of Krox20 staining in a non-cell autonomous manner in the Noggin cap. In Fig. 2D, the Noggin-injected cap was marked with FIDx, and in Fig. 2E, the Wise cap was marked with lacZ, as lineage tracers;

Fig. 3 shows the expression of Wise in chick and *Xenopus* embryos;

Figs. 3A-3D shows the *in situ* hybridization of chick embryos. Wise is expressed in the surface ectoderm from the level of presomitic mesoderm to the posterior end at stage 10 (Fig. 3A). Higher transcript levels are detected at stage 11 (Fig. 3B), which refine to a small posterior domain by stage 12 (Fig. 3C). In Fig. 3D, a section of Fig. 3A, in the vicinity of Hensen's node shows Wise transcripts confined to the surface ectoderm (se);

Fig. 3E shows the RNase protection of *Xenopus* embryos with stages noted above each lane. Wise is first detected at an early gastrula stage, and the expression persists into tadpole stages. ODC is a loading control;

Figs. 3F and 3G shows the whole mount *in situ* hybridization to *Xenopus* embryos. At stage 15 (Fig. 3F), Wise is expressed in the surface ectoderm at all anterior-posterior levels. The expression is strongest at the edge of the neural tube. At tadpole stages (Fig. 3G, stage 40), expression is localized in epibranchial placodes, lateral lines, and along the dorsal fin;

Fig. 4 shows changes in neuronal markers after blastomere injection of Wise RNA and Wise antisense morpholino oligos;

Figs. 4A-4L shows *in situ* hybridization with neural markers in stage 16-21 *Xenopus* embryos following single blastomere injections of Wise RNA (Figs. 4B, 4E, 4H, and 4K) at the 8-cell stage or antisense morpholino oligos (Figs. 4C, 4F, 4I, and 4L) at the 4-cell stage. The left panels (Figs 4A, 4D, 4G, and 4J) indicate control embryos. In most embryos, lacZ (blue staining) was co-injected as a lineage tracer. Injected sides are to the left. Probes were Sox3 (Figs 4A-4C), En2 (Figs. 4D-4F), Krox20 (Figs. 4G-4I), and Slug (Figs. 4J-4L). In Wise RNA injected embryos, the neural markers were generally displaced posteriorly. Ectopic induction of Krox20 and Slug can be seen in the forebrain region (Figs. 4H and 4K). In embryos injected with antisense morpholino oligos, these markers were unchanged;

Figs. 4M and 4N show the transverse sections at stage 16 after blastomere injection of either Wise RNA (Fig. 4M) or Wise antisense morpholino oligo (Fig. 4N). In Fig. 4M, the neural plate on the injected side was greatly expanded, which is revealed by Sox3 staining (dark blue, *). Conversely, in the morpholino oligo-injected embryo (Fig. 4N), the surface ectoderm is thicker on the injected side (left, *) in comparison to the right control side;

Fig. 5 shows the anterior defects after blastomere injection of Wise RNA or morpholino oligo;

Figs. 5A-5L shows *in situ* hybridization with the cement gland marker XCG at stage 16-20 (Figs. 5A-5C) and morphological phenotypes of cement gland at stage 26-40 (Figs. 5D-5F) or eye at stage 35-36 (Figs. 5G-5I), in control embryos (Figs. 5A, 5D, and 5G), Wise RNA injected embryos (5B, 5E, 5H), and morpholino oligo injected (Figs. 5C, 5F, and 5I) embryos. Blue staining shows co-injected lacZ lineage tracer. Over-expression of Wise resulted in formation of

larger cement glands (Fig. 5C). Eye formation is consistently blocked by injection of both Wise RNA (Fig. 5H) and the morpholino oligo (Fig. 5I);

Fig. 5J shows *in vitro* translation of Wise in the presence of the Wise morpholino antisense oligo. Lane 1; translation of Wise protein without morpholino oligo. Lanes 2-7; translation in the presence of the Wise morpholino oligo at concentrations of 0.1 nM, 1 nM, 10 nM, 100 nM, 1 μM, 10 μM, respectively. Lane 8; translation in the presence of control morpholino oligo at the concentration of 10 μM. Wise translation is partially blocked at concentration of 1 μM, and completely blocked at 10 μM;

Fig. 5K shows the rescue of the eye defect resulting from injection of the morpholino oligos by co-injection of Wise RNA;

Figs. 5L-5N are the phenotypes of embryos following injection of Wise morpholino oligos throughout the whole embryo. 5L shows the range of cyclopic eye and short trunk phenotypes induced by the oligos in comparison to the control embryo (left). Section of control (Fig. 5M) and morpholino-injected (Fig. 5N) embryos at the level of eye. In the Wise morpholino-injected embryos, eyes are positioned very close to the neural tube;

Fig. 6 shows that Wise requires components of the Wnt pathway for En2 induction and stimulates translocation of β-catenin to the nucleus;

Figs. 6A-6C show the RT-PCR of Noggin treated animal caps assayed for En2 (en) induction. NCAM is used as a pan neural marker and Efl a is a loading control. Fig. 6A shows the induction of En2 by Wnt8 or Wise RNA is blocked by dominant-negative (dn) Frizzled 8 ΔFz8. Fig. 6B shows the induction of En2 is blocked by dn-Wnt8 (Wnt8), dn-Dishevelled ΔDsh(dd1), GSK3 and dn-Lef1 (LEFΔN). Fig. 6C shows the induction of En2 requires signaling components of the canonical Wnt pathway but not the planar cell polarity (PCP) pathway. Wise-

mediated En2 induction is abolished by ΔDsh(dd1), a dominant negative form of Dishevelled for both pathways, and ΔDsh(DIX), which blocks the canonical pathway. ΔDsh(DEP) blocks the PCP pathway but has no effect on Wise induction of En. ΔDshΔN specifically activates the PCP pathway but fails to induce En in the absence of Wise, although full length dishevelled (Dsh) is able to do so;

Figs. 6D-6G show the staining for sub-cellular localization of endogenous β-catenin detected immunocytochemically in *Xenopus* animal caps following RNA injection of: Fig. 6D, TCF3; 6E, Wnt8+TCF3; Fig. 6F, Wise+TCF3; and Fig. 6G, β-catenin+TCF3. Wnt8 (Fig. 6E) and Wise (Fig. 6F) promoted accumulation of nuclear β-catenin;

Fig. 7 shows how Wise affects Wnt signaling;

Figs. 7A-7C show the secondary axes induced by Wnt8 are blocked by Wise. Injection of Wnt8 RNA into a ventral vegetal blastomere of 4-8-cell stage embryos induces complete secondary axis formation (Fig. 7A). Co-injecting Wise blocks formation of Wnt8-induced secondary axis (Fig. 7B), similar to the effect obtained by co-injection of a dominant negative Dishevelled, ΔDsh(DIX) (Fig. 7C);

Fig. 7D shows Wise functions extracellularly to block induction of siamois and Xnr3 by the Wnt pathway in ventral marginal zones. Wise blocks the ability of Wnt8 to induce Siamois and Xnr3, but does not interfere with the ability of Dishevelled (Dsh) or β-catenin (β-cat) to induce these markers;

Figs. 7E and 7F show that Wise acts as Wnt inhibitor and induces head development in the incomplete secondary axis. When BMP signaling is blocked at the ventral marginal zone by injection of a truncated BMP receptor (tBR), an incomplete secondary axis is formed (Fig. 7E).

Co-injection of tBR and Wise induces a complete secondary axis with eyes (arrows) and cement gland (Fig. 7F);

Figs. 7G-7I show that Wise blocks cell movements in Activin-treated animal caps. Control animal caps (Fig. 7G) undergo gastrulation-like movements in the presence of Activin (Fig. 7H). In Wise injected animal caps, elongation is blocked (Fig. 7I), but mesoderm induction occurs;

Fig. 8 shows that Wise interacts with the extracellular domain of Frizzled 1, 3, 7, 8; and Western blotting of COS cell extracts from cells transfected with epitope tagged protein variants. The relevant constructs transfected into COS cells that were used to prepare each extract are listed at the top of each column;

Fig. 8A shows that Frizzled binds to Wise, as well as to Wnt8;

Fig. 8B shows that Wnt8 interacts with Fz1 but not with Wise; and,

Fig. 8C shows that Wise interacts with Fz1, Fz3, Fz7, and Fz8;

Figs. 8A-8C, in the top panels are controls showing that the Myc-tagged versions of each protein are present and recognized by the anti-Myc antibody. The middle panels are controls showing the presence of proteins tagged with FLAG and recognized by the anti-FLAG antibody. The bottom panels illustrate results of immuno-precipitation using the anti-Myc antibody and Western blotting with anti-FLAG to show protein interactions. The antibodies used in each set of experiments are indicated at the left;

Fig. 9A is a schematic showing the gene structure for Wise and Sost;

Fig. 9A depicts the Neo-LacZ cassette insertion into Exon 1, which is separated from Exon 2 by an intervening intron sequence;

Fig 9B shows mouse Wise and Sost polypeptide sequences;

Fig. 9C shows Wise, Sost, and Hox A and B genes in chromosomes;

Fig. 9D illustrates the family tree map showing the relatedness of Wise and Sost to other cysteine knot family members;

Fig. 9E shows the family of cysteine knot proteins and their aligned polypeptide sequences;

Fig. 10 is a model of the Wise and SOST Exons, which express the cysteine knot structure. It depicts the 200 bp of Exon 1 and the 400 bp of Exon 2;

Fig. 11 shows the effects of Sost and Wise polypeptides on *Xenopus* embryonic development;

Fig. 11A shows that Wise and Sost defects lead to morphological abnormalities in *Xenopus* tadpoles;

Fig 11B is a table showing Wise and Sost effects on Noggin and Wnt8 expression in embryos;

Fig. 11C depicts Sost effects for Wnt8 and β-catenin with VMZ and DMZ;

Fig. 11D shows electrophoretic patterns for NCAM, En2 and EF1-α;

Fig. 11E shows electrophoretic patterns for Siamois, Xnr3, and EF1-α;

Fig. 12 shows the effect of the absence of a functional Wise polypeptide molecule upon ophthalmic development in Wise knockout mice, wherein ophthalmic and eye abnormalities developed in these mice. Immunodetection of Wise protein production in murine retinal regions was used to determine the efficacy of induced Wise mutation;

Fig. 12A shows whole eye mounts containing retinas or sections that were stained with anti-Wise antibody and FITC-conjugated second antibody;

Fig. 12B shows that in wild type mice, anti-Wise reactivity was detected as secreted Wise protein in the ganglion cell and optic fiber layers and in rods and cones. However, Wise mutant mice eyes lacked detectable anti-Wise peptide reactivity, indicating absence of Wise from tissues of these mutant mice. The Wise mutant mice appeared to have lost the majority of the optic nerve fibers and had increased rod and cone layers in the retina. Wise protein was found in the inner plexiform layer, ganglion cells and fibers, and in the rods and cone layer of a 2.5 month mouse retina;

Fig. 12C shows immunoflurescence patterns for Wise, Pax6 and 2H3 in tissue cross-sections;

Fig. 13 shows results of bone staining and bone mineral density (BMD) measurements;

Fig. 13A depicts hematoxylin and eosin (H&E) staining of cross-sections of bone tissue from 16 to 18 days post cortum (DPC) mice;

Fig. 13B illustrates the same bone regions as Fig. 13A; however, Fig. 13B left shows staining with S-35 radiolabel attached to Sost RNA probes, wherein Sost is located in osteoblasts in 16 to 18 DPC mice. Fig. 13B right also shows staining with anti-Wise peptide primary antibody and FITC-conjugated secondary antibody, and localization of Wise in hypertrophic and prehypertrophic proliferating chondrocytes;

Fig. 13C shows graphical depictions of bone density measurements and total bone weight measurements, respectively. Fig. 13C left shows that observable significant differences in BMD measurements between Wise mutant and wild type mice at certain ages. Fig. 13C right depicts total bone weight measurements. Fig. 13 generally shows both Sost and Wise genes appear to affect bone cells. Sost is expressed in osteoblasts. In contrast, Wise is expressed in periosteum, chondrocytes (proliferating, prehypertrophic and hypertrophic), but not in the growth plate;

Fig 14A shows a bilateral view of two molars with developing tooth buds on hemotoxylin and eosin staining of a tooth cross-section;

Fig 14B shows a bilateral view of two molars with developing tooth buds with S-35 RNA probe-labeled Sost staining;

Fig 14C shows a bilateral view of two molars with developing tooth buds stained with S-35 RNA probe-labeled Wise stain for purposes of detailing the layers of the dental follicle surrounding the molar teeth;

Fig 14D shows a molar tooth bud at a higher magnification with a bilateral view of two molars on hematoxylin and eosin staining of a tooth cross-section;

Fig 14E shows a molar tooth bud at a higher magnification stained with S-35 RNA probe-labeled Sost stain for purposes of detailing the osteoblasts and trabecular bone adjacent to the molar tooth;

Fig 14F shows a molar tooth bud at a higher magnification stained with S-35 RNA probe-labeled Wise stain for purposes of detailing the dental follicle layers;

Fig 14G shows a bilateral view of two molars on hematoxylin and eosin staining of a tooth cross-section, an incisor tooth staining patterns, and the morphological features of two incisors, with the nasal crest between them, tongue, and hair follicles of the whisker pad;

Fig 14H shows incisor tooth staining patterns with S-35 RNA probe-labeled Sost stain for purposes of detailing the osteoblasts of trabecular bone;

Fig 14I shows incisor tooth staining patterns with S-35 RNA probe-labeled Wise stain, prominent Wise staining of incisors, hair follicles and the whisker pad are also stained with Wise labeled RNA probes;

Fig 14J shows X-ray photographs of incisor teeth in the maxilla (upper jaw) regions of the wild type mice, utilizing a 120 strain genetic background;

Fig 14K shows X-ray photographs of incisor teeth in the maxilla (upper jaw) regions of the Wise mutant mice utilizing a 120 strain genetic background, the Wise mutant jaw possesses an additional incisor tooth (i') not present in the wt mouse shown in Fig 14J, the additional tooth may orginate from either an additional tooth bud or, alternatively, from a bifurcation of the original incisor;

Fig 14L shows the patterning in molar teeth observed in a wt mouse against a C57BL6 genetic background;

Fig 14M shows the patterning in molar teeth observed in a Wise mutant mouse against a C57BL6 genetic background, the additional M1 molar in the Wise mutant is present compared to the M1, M2, and M3 molars present in the wt mouse in Fig 14L;

Fig 14N shows the patterning in molar teeth observed in a wt mouse against a 129 background; and

Fig 14O shows the patterning in molar teeth observed in a Wise mutant mouse against a 129 background, abnormalities are present compared to the wt mouse of Fig 14N.

DETAILED DESCRIPTION

The present invention relates to a family of nucleic acid molecules, which encode polypeptides that bind to LRP and likely regulate the Wnt pathway and, resultingly, regulate bone deposition. The polypeptides will also regulate ocular and tooth development. The present invention further relates to proteins and polypeptides, or amino acid sequences, expressed from the family of nucleic acid molecules, which regulate bone deposition through LRP interaction.

In particular, a nucleic acid molecule family, which includes the Wise and Sost genes, can be used with the present invention, as well as the family of amino acid sequences expressed therefrom. When the above family of amino acid sequences, including Wise and Sost, are allowed to bind to an LRP protein, bone deposition is regulated. When the family of amino acid sequences are prevented from binding to an LRP protein, deposition of bone will increase.

Antisense RNAs or oligonucleotides can be used to block translation of mRNA related to or translated from the above described nucleic acid molecules—in particular, the LRP binding family of amino acid sequences and polypeptides can cause increased bone deposition and likely activate the LRP/Wnt pathway. Similarly, inhibitor peptides and polypeptides prevent the above family of amino acid sequences from binding to an LRP to thereby increase bone deposition. As such, the present invention includes the above listed methods, nucleic acid molecules, amino acid sequence or polypeptide molecules, as well as related compositions and methods designed to prevent or inhibit binding by the LRP binding protein family to LRP. These tools can also be used to effect phenotypic changes. Specifically, mutants versions of Wise or Sost will cause phenotypic changes. Kits are described for detection of the above native nucleic acid molecules and amino acid sequence molecules. Kits are described for detection of mutant or variant forms of the aforementioned nucleic acid molecules, detection of expressed polypeptides or proteins, and measurement of corresponding levels of protein expression.

The novel Wnt inhibitor, Wise, has been isolated in the present invention. Wise affects craniofacial anterior-posterior patterning. The biochemical function of craniofacial A-P patterning is generally addressed in the present invention. Previously, it was shown that when chick somites were transplanted to more anterior locations, an anterior shift in Hox gene expression was observed. This shift in expression resulted in a posteriorization of the more

anterior neural tissue. A screen for molecules involved in this process lead to the isolation of Wise. Wise is a secreted molecule that, until now, has not been shown to share much homology to any known molecules. Its gene structure contains two exons (200 and 400bp) with a large 2.5Kb intron (Fig. 10). The second exon encodes a cysteine knot motif, which bears some homology to known DAN, and CCN family members (Figs. 9, 10, 11). Wise is mapped to Human chromosome 7p21.1, which in turn is linked to the HoxA cluster by 10.6Mb (Fig. 9C). The four mammalian Hox clusters are thought to have evolved from a single cluster, as in *Drosophila*, therefore other clusters were searched for a possible Wise family member. Nothing was found that linked to the HoxD cluster, however, it was found that both HoxB and HoxC clusters had an ORF that was examined further. The HoxC cluster ORF, at 4Mb upstream shares homology to the CCN family. The HoxB cluster contained an ORF at 5Mb upstream. The HoxB ORF encodes a known gene, Sost. Sost was positionally cloned because of a familial mutation affecting bone density. Sost and Wise both share the same gene structure, and produce a secreted protein whose second exon (70% homologous) encodes for a cysteine knot. Unlike the known cysteine knot from DAN or CCN family members, Wise and Sost cysteine knots contain 8 cysteines instead of 9 like CCN and DAN families. Other molecules, Mucin2 and VWF have cysteine knots containing 10 cysteines, but are arranged in a manner similar to both the CCN and DAN family. DAN and CCN cysteine knots share about 50% homology to those of Wise and Sost. In addition to the cysteine knot domain, CCN proteins also encode for Insulin binding, Von Willderbrand, and TSP1 domains. However, the DAN family appears to only encode for a cysteine knot domain. Other genes that encode a cysteine knot domain include Slits, VWF, Mucins, and NDP.

A new Wise family member, Sost, has been characterized herein. Both Wise and Sost are linked to a Hox cluster further supporting Hox cluster duplication hypotheses. Sost functions like Wise to inhibit the Wnt pathway, however, unlike Wise, Sost is unable to induce En2 expression. The inability to induce En2 is very similar to other cysteine knot family members, like CTGF and Nov.

A family of genes and related proteins or polypeptides was isolated, which likely bind to LRP and likely regulates the LRP/Wnt pathway and causes regulation of bone deposition. The family of genes includes NDP, Dan, Caronte, PDGF, Wise, Sost, Cereberus, Gremlin, CTGF, Soggy, Dkk1, Cyr61, Dkk2, Dkk3, Dkk4, Nov, Mucin, Slit, OH, WISP, and CCN. Proteins expressed therefrom form a related amino acid sequence family. These nucleic acid molecules include sequences identified as SEQ ID NOs 1-44, 96-103, 105, 108, 110-113, and 126-128, and amino acid sequences identified as SEQ ID NOs 45-95, 104-107, 109, 114-125. When the above genes of the family are turned off, or mutagenized, the LRP pathway typically is not regulated and deposition of bone will increase. More particularly, the gene-encoded proteins do not bind to LRP, resulting in increased bone deposition. The gene-expressed proteins can be blocked to prevent regulation of the LRP pathway. Thus, the present invention relates to nucleic acid molecules and amino acid sequences and other tools and methods used to inhibit, block or deactivate binding of the LRP binding family to LRP. Inhibition of Wnt signaling can occur with resultant blocking or deactivation of the LRP binding family to LRP.

Related to this, it is known that mutant Wise and Sost polypeptides cause phenotypic changes in bone deposition, ocular development and tooth development. Regardless of interaction with LRP it is determined that mutants of Sost or Wise, or antibodies which attach to Sost or Wise, will cause phenotypic changes.

The above gene family and related proteins can not only be characterized as binding to or blocking binding to LRP, but as a gene family that expresses related proteins that each possess at least one cysteine knot. The cysteine knot is generally formed by 8 cysteine residues, which are readily conserved. However, other knots may have fewer or more residues. Typically, a guanine is part of the structure and conserved. Guanine will, along with two other amino acids, separate two cysteines located in one arm. For example, the gene family contains the genes Sost, Wise, Dkk1, Dkk2, OH, WISP, and CTGF. These genes include an exon region (*e.g.*, Exon 2), which expresses a protein or amino acid sequence molecule, which has a cysteine knot and binds to LRP.

Wise genes and polypeptides that have been specifically isolated, including wild types, alleles, mutants, synthetic versions and any other related homologous nucleic acid sequences, are used herewith. Wise contains two exons, with Exon 2 considered the most important. Exon 2, when expressed, produces a polypeptide that has a cysteine knot.

The present invention includes the LRP binding family of polypeptide molecules, such as Wise, Sost, Dkk1, Dkk2, and CTGF, that binds to LRP, which will, in turn, likely bind to Wnt. The LRP proteins and related genes will include LRP 1-11, and Arrow. LRPs that have been found to be specifically related to the present include LRP1,2,5, and 6. Available LRP nucleic acid sequence, are SEQ ID NOs 29-43, polypeptide SEQ ID Nos 67-88.

The present invention also relates to antisense RNA (asRNA) complementary to an mRNA from the LRP binding nucleic acid family, in particular Wise and Sost, whereby the asRNA will inhibit the members. An RNA may also be used to induce post-transcriptional gene silencing. This RNAi will cause translation of the gene family to cease. Any RNA/DNA that is complementary to the mRNA related to the discussed gene family, can be used to destroy a

family member. Other mutants include point frame shift, deletion, truncated, base substituted, and less of function mutations. The loss of function mutations are made with a stop codon. Additionally, a polyclonal or monoclonal anti-peptide antibody to the cysteine knot antigenic region may be used for detection or inhibition. This antibody would inhibit interaction with LRP. The antibody can also be directed to the entire Wise or Sost polypeptide. A point mutation may be made in a nucleic acid sequence member of the gene family, whereby the expressed protein or polypeptide cannot bind LRP. Alternatively, an antisense oligonucleotide can be used, which will prevent translation of mRNA and thereby inhibit binding to LRP. An anti-polypeptide antibody can be used to bind to LRP and prevent binding with a cysteine knot protein, preferably functioning by a steric hinderance mechanism.

Mutant alleles of the LRP binding gene family can express a protein or amino acid sequence that will not bind LRP and thereby increase bone deposition. As discussed, expression of such a mutant can be therapeutically desirable, especially when used as a method for producing stronger bones or increased recovery from bone disease. Thus, the present invention relates to mutants of the listed gene family. The present invention includes administration of such mutant polypeptide products that can result in increased bone deposition.

Antibodies, which specifically bind to the above proteins and probes for isolating the proteins or nucleic acid molecules, are further part of the present invention. Fab fragments can be derived from the antibodies. Yet another part of the present invention relates to methods for increasing bone deposition by preventing the protein family from binding to an LRP and, in turn, likely regulating the Wnt pathway. The invention includes methods for blocking expression of the nucleic acid molecules, and methods for preventing the amino acid sequences from binding to Wnt or LRP. Kits are also part of the invention which detect mutants and non-mutants of the

nucleic acid molecules, and their expressed amino acid sequences or polypeptide molecules. As such, the present invention includes diagnostic and therapeutic methods and kits for the prediction, assessment, and regulation of bone deposition.

Nucleic acid sequences complementary to the previously listed nucleic acid molecules, preferably the mutants, of the gene family may also be used with the present invention. As expected, such a complementary nucleic acid sequence is one that can be expressed to form a protein or amino acid sequence that binds to LRP and regulates bone deposition. The complementary sequence can also be used to prevent binding of LRP and, thus, increase bone deposition. A complementary nucleic acid sequence from a member of the LRP binding gene family can be made to produce an expressed polypeptide that can impact binding to LRP and ultimately regulate bone deposition. Further, degenerate variants of the sequences may be used. Also, isolated nucleic acid molecules that encode the LRP binding family protein or amino acid sequence may be used in the present invention.

Nucleic acid molecules homologous to the wild type nucleic acid molecules, and the mutant nucleic acid molecules, may be used to regulate or cause increased bone deposition. The homologous nucleic acid molecules are identified using a BLAST (Basic Alignment Search Tool) (NCBI) sequence method. Suitable homology will include those nucleic acid molecules that are 50% homologous to the listed mutant alleles, or non-mutants. More preferably, the homology will be 60% and, even more preferred, 75% homologous to the mutant alleles, or non-mutants. The most preferred homologous nucleic acid molecule will be 90% homologous to the mutant alleles, or non-mutants (*i.e.* wild type), in particular, Wise, Sost, and mutants thereof. Homologous nucleic acid molecules may be derived from animals, including, but not limited to, humans, non-human mammals, amphibians, and insects.

Isolated nucleic acid sequences, such as oligonucleotides, can be derived from the nucleic acid molecules, which are the active portions of the molecules, to bind with LRP, mRNA, or ultimately prevent binding of the LRP protein. Such oligonucleotides are a part of the present invention. The active region, which forms the oligonucleotide molecules, includes the cysteine knot region. More particularly, a region which expresses a cysteine knot sequence that binds to LRP can be used. Conversely, oligonucleotides related to the mutant forms of the genes can be used to prevent regulation of bone deposition.

Expression vectors, which regulate bone deposition, can be formed that contain the above-discussed nucleic acid molecules, using known procedures. A promoter can be operably linked to the isolated nucleic acid molecule to form the expression vector. Any promoter can be used which causes expression of the nucleic acid molecule, and can be switched on and off. It is further preferred to include a marker with the vector. Suitable vectors include DNA vectors, plasmid vectors, and shuttle vectors.

Vectors are formed from both the isolated nucleic acid sequences and the mutant versions of the isolated nucleic acid sequences. The vectors include expression, cloning, and viral vectors. Other available vectors include fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-hybrid vectors, sequencing vectors, and cloning vectors. Also, prokaryotic and eukaryotic vectors may be used. Specific prokaryotic vectors that may be used in the present invention include pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280, pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT. Specific eukaryotic vectors that may be used herein include pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo,

pSVK3, pSVL, pMSG, pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis. As mentioned, a variety of promoters may be used with the vector, as well as any of a variety of selectable markers. Available markers include antibiotic resistance genes, a tRNA gene, auxotrophic genes, toxic genes, phenotypic markers, colorimetric markers, antisence oligonucleotides, restriction endonuclease, enzyme cleavage sites, protein binding sites, and immunoglobulin binding sites. Specific selectable markers available include LacZ, neo, Fc, DIG, Myc, and FLAG.

Once the vectors are formed, they can be used to transfect a host cell, whereby a transgenic host cell will be produced that incorporates a vector that expresses the selected nucleic acid molecule, which prevents or causes bone deposition through interaction with the LRP. Such bone deposition may likely involve interaction with the Wnt pathway. Methods for transfecting the host cell are well known to those of skill in the art, and comprise culturing the vectors with the host cells.

The host cell can be derived from any of a variety of eukaryotic cell origins, including animal-, mammalian-, amphibian-, or insect-derived cells. More preferably, the host cells are derived from non-human mammals and humans. The preferred host cell is an osteoblast/osteoclast, chrondocytes.

Any of a variety of host cells, including prokaryotic and eukaryotic cells, can be transfected with the vectors previously mentioned. Prokaryotic host cells include Gram-negative and Gram-positive bacteriums may be transfected with any of the variety of the vectors previously mentioned. Available bacteriums include Escherichia, Salmonella, Proteus, Clostridium, Klebsiella, Bacillus, Streptomyces, and Pseudomonas. A preferred Gram-negative bacterium is Escherichia coli. Eukaryotic vectors can be used to transfect eukaryotic host cells

including yeast, plant, fish, mammalian, human, mouse, frog, or insect cells. Specific host cells that can be transfected include ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, chrondocytes, and human or mammalian bone marrow stroma. As such, the present invention includes host cells transfected with any of the previously mentioned vectors.

A transgenic animal can be formed using the present invention. In particular, transgenic non-human animals can be formed by insertion of the wild type or mutant nucleic acid molecules into cells of a host animal. The insertion of nucleic acid molecules into host animal cells can occur by a variety of methods including but not limited to transfection, particle bombardment, electroporation, and microinjection. Insertions can be made into germ line, embryonic, or mature adult host animal cells.

The proteins or amino acid sequences expressed by the nucleic acid molecules, related mutants, and the listed nucleic acid molecules can activate LRP/Wnt and can be isolated and purified. Additionally, the mutants, asRNA molecules, as oligonucleotides, and anti-peptide antibodies can be developed and used to prevent binding to LRP or binding of Wise or Sost. The proteins or amino acid sequences from both the non-mutant and mutant nucleic acid molecules can also be isolated and purified. Such isolation and purification include known procedures and methods, including affinity chromotography or purification, as well as other methods. The isolated proteins include those listed herein. Additionally, suitable proteins or amino acid sequences include those that bind to LRP and Wnt, and prevent or cause activation, dependent upon the desired outcome.

Proteins, which are 90% homologous with the polypeptides lised in SEQ IDs are also included. As would be expected, polypeptides or proteins that are 50% homologous to the

polypeptides may also be used, with proteins 60% homologous more preferred. A polypeptide that is 75% homologous to SEQ ID NOs 45-95, 104-107, 109, and 114-125 is even more preferred. As such, any of a variety of polypeptides may be used, as long as they are expressed by an LRP binding family member, Sost Wise, or homologous nucleic acid molecule, and prevent influence Wnt, Bone deposition, tooth development or ocular development. More preferably, mutants will be used. Resultingly, the proteins will cause increases of bone deposition to occur. Non-mutant, homologous amino acid sequences may be used. The extent of homology will be identical to that previously described above. Thus, sequences that are 50% homologous to the proteins or amino acid sequences may also be formed. More preferably, the sequences will be 75% homologous, and even more preferably, 90% homologous to the proteins.

Probes, which can be used to isolate, identify, and characterize the above proteins and/or genes, can be formed from such proteins or genes. The probes include cDNA, mRNA, and monoclonal and polyclonal antibodies. All the probes are formed using known procedures. Probes, which are 50% homologous to the proteins or amino acid sequence, may also be formed. More preferably, the probes will be 75% and, even more preferably, 90% homologous to the above proteins. The formula used to determine the homology of the probes is a BLAST sequence.

Antibodies, which specifically bind to the above-listed proteins, are part of the present invention. Additionally, hybridomas that produce such antibodies are used herewith. In addition to protein probes, cDNA probes may be formed, which are comprised of isolated nucleic acid molecules previously discussed. As such, any antibody that binds specifically to a Wnt binding family member, may be used. Antibodies that selectively bind to an epitope in the receptor-

binding domain of the LRP/Wnt binding mutant protein may also be used. A non-mutant or wild type epitope may also be used.

A kit for detecting a LRP binding gene, or related nucleic acid molecule, can be formed. The kit will preferably have a container and a nucleic acid molecule, which includes any of the mentioned sequences.

A kit for detecting a LRP binding protein or amino acid molecule can also be formed. The kit will preferably have a container and a nucleic acid molecule, which includes any of the mentioned sequences.

The family of genes and proteins can be used as tools to develop asRNAs and polypeptides, which regulate LRP/Wnt.

Neural patterning in embryogenesis involves signaling between the neural plate and surrounding tissues. To investigate this process, a functional screen was performed using a cDNA library derived from chick tissues surrounding the neural tube. Activities that alter anteroposterior (A-P) character of neuralized *Xenopus* animal caps were assayed for, and a novel gene was identified, Wise, which was expressed in surface ectoderm. Wise encodes a secreted protein capable of inducing posterior neural markers. Importantly, the phenotypes arising from ectopic expression of Wise resemble those affected when Wnt signaling is altered. Induction of posterior markers by Wise likely requires components of the canonical Wnt pathway, showing that it activates the Wnt signaling cascade. In contrast, in other assays, such as secondary axis induction, Wise inhibits Wnt signaling. Wise protein interacts with LRP receptors, but not with Wnt, demonstrating that Wise is a novel ligand for LRP, which either activates or inhibits the signaling pathway. Hence, Wise differentially influences the Wnt signaling cascade in a context-

dependent manner. These activities provide a novel mechanism that integrates and modulates the balance of Wnt signaling.

The following are definitions for terms used herein.

An animal cap is a pigmented animal hemisphere of the amphibian blastula. The vegetal becomes endoderm and part of the animal pole becomes ectoderm. In most animal oocytes the nucleus is not centrally placed, and its position can be used to define two poles. That nearest to the nucleus is the animal pole, and the other is the vegetal pole, with the animal-vegetal axis between the poles passing through the nucleus. During meiosis of the oocyte, the polar bodies are expelled at the animal pole. In many eggs, there is also a graded distribution of substances along this axis, with pigment granules often concentrated in the animal half and yolk region, when present, largely situated in the vegetal half.

The anterior-posterior axis is the body axis extending from the anterior to the posterior pole of a bilaterally symmetric embryo (or animal).

Blastomere is one of the cells produced as the result of cell division and cleavage, in the fertilized egg.

Blastula is the stage of embryonic development of animals near the end of cleavage but before gastrulation. In animals where cleavage or cell division involves the whole egg, the blastula usually consists of a hollow ball of cells.

Bone is continually deposited by osteoblasts. Normally, bone deposition and absorption are equal.

DNA cassette is a deoxyribonucleic acid (DNA) sequence that can be inserted into a cell's DNA sequence. The cell in which the DNA cassette is inserted can be a prokaryotic or eukaryotic cell. The prokaryotic cell may be a bacterial cell. The DNA cassette may include one

or more markers, such as Neo and/or LacZ. The cassette may contain stop codons. In particular, a Neo-LacZ cassette is a DNA cassette that can be inserted into a cell's DNA sequence located in a bacterial artificial chromosome (BAC). Such DNA cassettes can be used in homologous recombination to insert specific DNA sequences into targeted areas in known genes.

The ectoderm is the germ layer that gives rise to the epidermis and nervous tissue.

The endoderm is the germ layer that gives rise to the respiratory organs, gut, and the gut accessory glands.

Gastrula is the stage of embryonic developments in animals when gastrulation occurs, and follows the blastula stage.

Gastrulation is the process by which cells of the blastoderm are translocated to new positions in the embryo, producing the three primary germ layers.

The germ layer is defined as the main divisions of tissue types in multicellular organisms. Diploblastic organisms (*e.g.*, coelenterates) have two layers, ectoderm and endoderm; triploblastic organisms (*i.e.,* all higher animal groups) have mesoderm between these two layers. Germ layers become distinguishable during late blastula/early gastrula stages of embryogenesis, and each gives rise to a characteristic set of tissues, the ectoderm to external epithelia and to the nervous system, for example, although some tissues contain elements derived from two layers.

Mesoderm is defined as the middle of the three germ layers; which gives rise to the musculo-skeletal, vascular, and urinogenital systems, to connective tissue (including that of dermis) and contributes to some gland formation.

Neural plate is defined as a region of embryonic ectodermal cells, called neuroectoderm, that lie directly above the notochord. During neuralation, the neuroectoderm changes shape, so

as to produce an infolding of the neural plate (*i.e.,* the neural fold) that then seals to form the neural tube.

The neural tube is the progenitor of the central nervous system.

Somites are defined as the blocks of tissue in the trunk derived from the originally unsegmented paraxial mesoderm.

Small molecules are defined as regulatory polypeptide or nucleic acid molecules that cause detectable changes in protein-protein interaction systems that may also affect one or more phenotypic changes. Interaction systems include, but are not limited to, Wise and Sost protein interaction with LRPs, the Wnt pathway, Engrailed, and Frizzled. These small molecules may operatively function by structural similarity to and competitive inhibition with native molecules *in vitro* or *in vivo*. Phenotypic changes may include observed changes in such parameters as bone deposition or bone mineral density, tooth development, and ocular development. Small regulatory polypeptide molecules include, but are not limited to, antibody fragments such as Fab, $F(ab)_2$, Fv, and antibody combining regions that bind with either Wise, Sost, or LRP; and shortened Wise, Sost or LRP polypeptide sequences. Small regulatory nucleic acid molecules include, but are not limited to, antisense RNA sequences that interfere with Wise, Sost, or LRP function; and truncated Wise, Sost or LRP nucleic acid sequences that encode shortened polypeptides that interfere with Wise, Sost or LRP function. An antisense Wise RNA is complementary to Wise sense RNA and operatively binds to it in a cell to prevent translation of native protein. A truncated Wise nucleic acid sequence encodes a shortened Wise polypeptide that can potentially competitively bind to LRP to prevent native Wise protein binding.

The vegetal pole is the surface of the egg opposite to the animal pole. Often the cytoplasm in this region is incorporated into future endoderm cells.

A vector is a self-replication DNA molecule that transfers a DNA segment to a host cell.

A host organism is an organism that receives a foreign biological molecule, including an antibody or genetic construct, such as a vector containing a gene.

Chimera is an individual composed of a mixture of genetically different cells. The genetically different cells of chimeras are required to be derived from genetically different zygotes.

Mutant is an organism bearing a mutant gene that expresses itself in the phenotype of the organism. Mutants include both changes to a nucleic acid sequence, as well as elimination of a sequence. In addition polypeptides can be expressed from the mutants.

Plasmids are double-stranded, closed DNA molecules ranging in size from 1 to 200 kilo-bases. Plasmids are vectors for transfecting a host with a nucleic acid molecule.

An amino acid (aminocarboxylic acid) is a component of proteins and peptides. Joining together of amino acids forms polypetides. Polymers containing 50 or more amino acids are called proteins. All amino acids contain a central carbon atom to which an amino group, a carboxyl group, and a hydrogen atom are attached. Polypeptides can be referred to when a protein is less than 500 amino acids.

A nucleic acid is a nucleotide polymer better known as one of the monomeric units from which DNA or RNA polymers are constructed, it consists of a purine or pyrimidine base, a pentose, and a phosphoric acid group.

A gene is a hereditary unit that has one or more specific effects upon the phenotype of the organism that can mutate to various allelic forms.

A polypeptide is a polymer made up of less than 50 amino acids.

Knockout is an informal term coined for the generation of a mutant organism (generally a mouse) containing a null allele of a gene under study. Usually the animal is genetically engineered with specified wild-type alleles replaced with mutated ones.

Allele is a shorthand form for allelomorph, which is one of a series of possible alternative forms for a given gene differing in the DNA sequence and affecting the functioning of a single product.

Wild type is the most frequently observed phenotype, or the one arbitrarily designated as "normal". Often symbolized by "+" or "wt."

Finally, the phenotypes observed in Wise mutants are similar to that of Sost mutants. Some phenotypes examined in the Wise mutant may explain Sost phenotypes, *i.e.* loss of retinal nerve fibers may be reason for optic nerve atrophy. Interestingly, it has been demonstrated that Wise inhibits the Wnt pathway by binding to an area encompassing the first two YWTD propeller domains of LRP. In humans the autosomal recessive disorder OPPG has been mapped to the area upstream of the first YWTD propeller domain of LRP5. Also, LRP5 is found to be expressed in osteoblasts and in retinal cells of *Xenopus* embryos. The same expression pattern was found for humans. It has been demonstrated that the loss of LRP5 function leads to very low peak bone mass and visual loss. Thus, early during bone development, Wise may be acting to inhibit Wnts through LRP5; and later, the inhibition of Wnts may be the function of Sost.

EXAMPLES

Example 1.

Functional screens in *Xenopus* were performed with the aim of identifying factors derived from tissues surrounding the neural tube that alter A-P patterning in Noggin-treated animal caps. Two clones were isolated, one encoded a truncated β-catenin and the other a novel secreted protein, which was named Wise. Isolation of the two clones is described below.

Fig. 1A provides an overview of how factors which impacted patterning were determined. Chick embryo somites, which are capable of transforming pre-otic rhombomeres into a more posterior neural tissue were collected together with overlying ectoderm and underlying endoderm. mRNA was collected from the tissue, which was then used to make a cDNA library. This provided a source of putative posteriorizing factors.

The cDNA library was made from stage 8-13, (Hamburger and Hamilton, 1951) chick embryos using tissues surrounding the neural tube (Fig. 1A) from axial levels capable of inducing Hoxb9 expression in grafting experiments (Itasaki et al., 1996). The library contained 250,000 un-amplified clones, and 50,000 of these were divided into 100 pools (500 clones per pool). For initial screening, 10 pools were mixed to prepare a single large DNA pool (5,000 clones) used to synthesize capped RNA. Size-selected (>1kb) cDNAs were directionally inserted into a modified 64T vector (Tada et al., 1998).

Xenopus eggs were obtained, fertilized, cultured, and injected with the synethized RNA, as previously described (Jones and Smith, 1999). In the first round of screening, 250 picogram (pg) of Noggin RNA and 12 nanograms (ng) of library RNA were injected into each blastomere of 2-cell state *Xenopus* embryo. To examine embryo phenotypes, RNA was injected into specific blastomeres, together with lacZ or FIDx (Molecular Probes) as a lineage tracer. Markers were assayed with *in situ* hybridization.

Following co-injection of Noggin RNA with pools of RNA from the cDNA library, the induction of posterior markers was monitored in animal caps by assaying for expression of En2, Krox20, and Hoxb9, which mark the midbrain, hindbrain, and spinal cord, respectively (Figs. 1B and 1C). Myosin was also used as a marker for mesoderm induction, which allowed focus on pools that influence neural patterning in the absence of mesoderm.

Explants (excised tissue) were processed for RT-PCR to detect region-specific neural markers. The primers for Eflα, NCAM, Otx2, En2, Krox20, Hoxb9, Myosin light chain and Muscle actin were used.

It was observed in pool 5, that En2 was induced in the absence of mesoderm (Fig. 1B). Successive rounds of sub-division and sib selection identified the clones responsible for this activity. From this pool, two distinct clones were isolated. One clone encoded an amino-terminally truncated form of β-catenin, a cytoskeletal component, and an intracellular target of the Wnt pathway. This result was consistent with data demonstrating that β-catenin has an ability to induce posterior neural markers in animal caps when co-injected with Noggin. The N-terminal truncation in the clone removed the first 87 amino acids, which included the sites for phosphorylation by GSK3β, which accelerated degradation of β-catenin protein. Therefore, the clone encoded a stable form of β-catenin able to stimulate Wnt signaling.

The second clone proved to encode a novel protein. Based on its characterization and relationship to Wnt signaling detailed in the study, the clone's gene was designated Wise (Wnt, inhibitor/activator in surface ectoderm). In the animal cap assays, injection of Wise RNA, together with Noggin, demonstrated that increasing concentrations of Wise progressively induced more posterior markers (En2 and Krox20) in the absence of mesoderm (Fig. 1C). Noggin equal to 500 pg and Wise equal to 150, 300, 600 and 1200 pg were injected. Wise alone

exhibited no neural-inducing activity (no NCAM induction) and no ability to induce mesoderm, as confirmed using Myosin (Fig. 1C), Brachyury, Wnt8, and Xhox3 as markers. It was observed that increasing amounts of Wise RNA (150, 300, 600, and 1200 pg) progressively induced more posterior neural markers in the presence of Noggin. Wise DNA and RNA were obtained using standard molecular biology methods. Sambrook et al., Molecular Cloning: a Laboratory Manual, 3rd ed., Cold Spring Harbor, N.Y., Cold Spring Harbor Laboratory Press (2001).

For explant recombination assays, 500 pg of Noggin was injected into one set of embryos and 1 ng of Wise injected into a separate set. For lineage tracing, either FIDx was injected, along with Noggin RNA, or 100 pg of lacZ RNA was co-injected with Wise. Caps were cut at stage 8, combined and cultured for assay at stage 25.

Example 2.

To isolate a frog clone, *Xenopus* stage 25 embryos were collected and a cDNA library was formed. This was used as a template for RT-PCR. Using degenerate primers, designed on the basis of conserved regions between chick and mouse Wise, ~500 bp fragments were sub-cloned into pBluescriptIIKS (Stratagene) and sequenced. The degenerate primers used were upstream, SEQ ID NO 129: 5'-GCTTT(T/T)AA(A/G)AA(C/T)GATGCCAC-3'; and downstream, SEQ ID NO 130: 5'-GTGAC(T/C)AC(T/G/A)GT(T/G)ATTTTGTA-3'. Two different clones in the frog were identified (XWise-A and XWise-B) presumably resulting from the pseudotetraploid *Xenopus* genome. For each clone, 5' and 3' flanking sequences were identified by PCR using a *Xenopus* stage 35 cDNA library. Standard PCR methods are described in U.S. Pat. No. 4,683,195; U.S. Pat. No. 4,683,202; Saiki et al., Science 230:1350-1354 (1985); Innis et al., PCR Protocols: A Guide to Methods and Applications, Academic Press, Inc., San Diego, Calif. (1990).

The predicted amino acid sequence of XWise-A was used for comparison with other species which are listed in Fig. 2A, which shows Wise as a conserved secreted protein. Various EST databases were searched, with the predicted amino acid sequences then aligned in Fig. 2A. The predicted amino acid sequence of Zebrafish, *Xenopus*, chick, mouse, and human Wise proteins were compared.

The predicted Wise protein, SEQ ID NO 45, consists of 206 amino acids and contains cysteine knot-like domains. These cysteine knot domains are found in a number of growth factors, as well as in Slit, Mucin, and CCN (Cef10/Cyr61, CTGF and Nov) family members (Bork, 1993). Among these, the C-terminal domain of the CCN family members showed the highest homology to Wise, but other motifs conserved within the CCN family were absent in Wise (Fig. 2B). Hence, Wise is related to, but not a member of, the CCN family. A homology search revealed that Wise showed the highest amino acid identity (38%) to Sclerostin (Sost), identified by positional cloning of the gene mutated in sclerosteosis (Brunkow et al., 2001).

Wise was further analyzed, as shown in Fig. 2B. The shaded boxes in Fig. 2B indicate three blocks (Δ1, Δ2, Δ3) deleted separately for functional analysis. This was done to investigate if the conserved regions were required for functional activity of Wise, three separate deletions were generated, and their ability to induce En2 expression in Noggin-injected animal caps was tested. The variant that deleted 19 amino acids outside of the CT domain (Δ1) retained the ability to induce En2. In contrast, two deletions corresponding to different parts of the Slit homology domain (Δ2 and Δ3) abolished the ability of Wise to induce En2, demonstrating that these regions were necessary for Wise function.

Example 3.

A signal sequence motif is present at the N-terminus of Wise, and its secretion was confirmed by Western blotting following expression of an HA-tagged version of the protein in *Xenopus* oocytes (Fig. 2C) and COS cells. More particularly, Wise was injected in an amount equal to 30ng/embryo. Western blot analysis detected HA-tagged Wise protein secreted into the medium following RNA injection into oocytes. Fig. 2C, related to the control of uninjected oocytes. Secretion of Wise was confirmed by expression of an HA-tagged version of the protein in *Xenopus* oocytes and COS cells. The protein was detected in both cell extracts and the culture medium (Fig. 2C). It was observed that Wise encoded a signal sequence motif at its N-terminus, suggesting that the protein is secreted.

Further, the ability of Wise to posteriorize neural tissue in a cell non-autonomous manner was tested by using a tissue recombination assay in which a Wise-expressing animal cap was combined with a noggin-expressing animal cap. It was found that both En2 and Krox20 were induced in discrete domains in the Noggin caps (Figs. 2D and 2E). Noggin was injected in an amount equal to 500 pg and Wise equal to 600 pg. Hence, it was determined Wise has the ability to induce posterior markers at a distance.

Subsequently, the ability of Wise to posteriorize tissues in a cell non-autonomous manner was tested. Recombination between Noggin-expressing and Wise-expressing animal caps were assayed for expression of Krox20 or En2, Figs. 2D and 2E respectively. Wise induced a ring of En2 (en) expression or patches of Krox20 staining in a non-cell autonomous manner in the Noggin cap. In Fig. 2D, the Noggin injected cap was marked with FIDx, and in 2E, the Wise cap was marked with lacZ as lineage tracers. Using a tissue recombination assay in which a Wise-expressing animal cap was recombined with a Noggin expressing animal cap, it was found that

both En2 and Krox20 were induced in the Noggin caps (Figs. 2D and 2E). As such, it was determined that Wise has the ability to induce posterior markers at a distance through the induction of Wnt.

Example 4.

The following Example analyzes the expression of Wise in chick and *Xenopus* embryos. Whole mount *in situ* hybridization analysis and sections in stage 9-12 chick embryos revealed that Wise was expressed in a dynamic manner in the surface ectoderm (Figs. 3A-3D). Expression was detectable first at stage 9. Expression was localized in the posterior surface ectoderm overlying the presomitic mesoderm, wherein somites were formed by stage 10-11 (Figs. 3A, 3B, and 3D). Figs. 3A-3D show *in situ* hybridization of chick embryos. Wise was expressed in the surface ectoderm from the level of presomitic mesoderm to the posterior end at stage 10, Fig. 3A. Higher transcript levels are detected at stage 11, Fig. 3B, which refine to a small posterior domain by stage 12, Fig. 3C. This is shown by the red stain in the Fig. 6. A section shown in Fig. 3D, in the vicinity of Hensen's node, showed Wise transcripts confined to the surface ectoderm (se). This is shown by the arrow. Expression decreased rapidly during stages 12-13, and resolved into a small posterior domain (Fig. 3D). This expression profile suggested that the original Wise cDNA was derived from the ectodermal part of the tissue used to make the library (Fig. 1A).

In an RNase protection assay, *Xenopus* Wise expression was weakly detected initially at gastrula stages (stage 10), and expression persisted into tadpole stages (Fig. 3E). Fig. 3E shows an RNase protection assay of *Xenopus* embryos with stages noted above each lane. Wise is first detected at an early gastrula stage, persisting into tadpole stages. ODC was a loading control. In later stage chick embryos, Wise was expressed in branchial arches and other specialized tissues,

including feather buds. A similar pattern was observed in *Xenopus* embryos. Wise was expressed in the surface ectoderm, but had a broader domain along the A-P axis, in comparison to chick (Fig. 3F). Figs. 3F and 3G show the whole mount *in situ* hybridization to *Xenopus* embryos. At stage 15 (Fig. 3F), Wise is expressed in the surface ectoderm at all anterior-posterior levels. The expression is strongest at the edge of the neural tube. At tadpole stages (Fig. 3G, stage 40), expression was localized in epibranchial placodes, lateral lines, and along the dorsal fin.

This data showed that Wise caused posterior development. It also showed the stages of development when Wise had the strongest effect.

Example 5.

The present Example relates to changes observed in neuronal markers after blastomer injections of Wise RNA and Wise antisense morpholino oligos (Fig. 4).

Morpholino antisense oligos were designed against the beginning of the coding region of *Xenopus* Wise-A and B. The sequences were: A (SEQ ID NO 131), 5'-AGCACTGGAGCCTTGAGACAACCAT-3'; B (SEQ ID NO 132), 5'-AGCAGTGAAGCCTTGAGACAACCAT-3'. A 1:1 mixture of these oligos was diluted in PIPES (5mM) buffered water and used for injection. *In vitro* translation of Wise RNA was inhibited at oligo concentrations of between 1-10 μM, which is equivalent to injecting 6-60 ng into one *Xenopus* embryo (1.2 mm diameter). For whole embryos, 30-60 ng of morpholino was injected, and for blastomeres (animal-dorsal or animal-ventral blastomere to target the surface extoderm) 13-33 ng was injected.

Fig. 4 shows changes in neuronal markers after blastomere injection of Wise RNA and Wise antisense morpholino oligos (Figs. 4A-L). *In situ* hybridization with neural markers in

stage 16-21 *Xenopus* embryos following single blastomere injections of Wise RNA (Figs. 4B, 4E, 4H, and 4K) at the 8-cell stage and antisense morpholino oligos (Figs. 4C, 4F, 4I, and 4L) at the 4-cell stage are shown. The left panels (Figs. 4A, 4D, 4G, and 4J) indicate control embryos. In most embryos, lacZ (blue staining) was co-injected as a lineage tracer. Injected sides were to the left. Probes were Sox3 (Figs. 4A-4C), En2 (Figs. 4D-4F), Krox20 (Figs. 4G-4I), and Slug (Figs. 4J-4L). In Wise RNA injected embryos, the neural markers were generally displaced posteriorly. Ectopic induction of Krox20 and Slug can be seen in the forebrain region (Figs. 4H and 4K). In embryos injected with antisense morpholino oligos, these markers were unchanged.

Figs. 4M and 4N show the transverse sections at stage 16 after blastomere injection of either Wise RNA (Fig. 4M) or Wise antisense morpholino oligo (Fig. 4N). In Fig. 4M, the neural plate on the injected side was greatly expanded, which is revealed by Sox3 staining (dark blue, *). Conversely, in the morpholino oligo-injected embryo (Fig. 4N), the surface ectoderm is thicker on the injected side (left, *) in comparison to the right control side.

To further evaluate the effects of Wise on development of the neural tube, RNA or DNA was injected into specific blastomeres at 4-16 cell stages. When Wise RNA injections were targeted to presumptive neural regions, expression of pan-neural markers (Sox3, NCAM) confirmed an expansion of the neural plate (Figs. 4B and 4M). A-P specific markers (En2, Krox20, and Slug) were generally displaced laterally and posteriorly and were frequently expanded (Figs. 4E, 4H, and 4K).

Identical results were obtained using DNA constructs for injection, where Wise expression commenced at mid-blastula stages under the control of a cytoskeletal actin promoter. Together, these changes in morphology and neural patterning demonstrated that ectopic expression of Wise disturbed extension and closure of the developing neural tube.

The disruption of neural tube morphogenesis made it difficult to assay for posteriorizing influences in whole embryos. However, when Wise injected cells were targeted to the forebrain region, ectopic expression of Slug and Krox20 was observed (Figs. 4H and 4K). This indicated that anterior forebrain cells acquired a more posterior character in response to Wise.

Localized injection of the morpholino oligo resulted in embryos developing with thickened ectoderm, which contrasted with Wise RNA injections where embryos developed with a thickened neural plate (Figs. 4M and 4N). Neural markers, such as Sox3, En2, Krox20, and Slug, were not obviously affected at early neural stages (Figs. 4C, 4F, 4I, and 4L). This verifies that Wise and Wise mutants influence A-P patterning.

Example 6.

Like Example 5, Wise RNA and morpholinos were injected into embryos. Injection of Wise RNA and morpholino oligos were observed to impact neural markers. Anterior defects after blastomere injection of Wise RNA or morpholino oligo were observed. Defects in anterior patterning, including a failure in eye formation, were observed at tailbud stages (Fig. 5H). Furthermore, expression of the cement gland marker XCG was specifically down-regulated in cells expressing Wise (Figs. 5B and 5E). Conversely, when Wise injected cells were distributed more ventrally, the ectopic induction of the cement gland and XCG expression was observed (Fig. 5B). Therefore, ectopic expression of Wise altered aspects of A-P patterning in embryos, as well as animal caps.

Figs. 5A-5L shows *in situ* hybridization with the cement gland marker XCG at stage 16-20 (Figs. 5A-5C) and morphological phenotypes of cement gland at stage 26-40 (Figs. 5D-5F). Hybridization with the eye at stage 35-36 is shown at Figs. 5G-5I. The controls are shown in Figs. 5A, 5D, and 5G. Blue staining shows co-injected lacZ lineage tracer. Over-expression of

Wise resulted in formation of larger cement glands (Fig. 5C). Eye formation is consistently blocked by injection of both Wise RNA (Fig. 5H) and the morpholino oligo (Fig. 5I).

To analyze the endogenous role of Wise in embryogenesis, the *Xenopus* cognate was isolated and used to design morpholino antisense oligonucleotides, which would specifically interfere with translation of Wise RNA. *In vitro* translation of Wise was blocked by the morpholino oligo, whereas a control oligo had no effect (Fig. 5J). Fig. 5J shows *in vitro* translation of Wise in the presence of the Wise morpholino antisense oligo. Lane 1 shows translation of Wise protein without morpholino oligo. Lanes 2-7 show translation in the presence of the Wise morpholino oligo at concentrations of 0.1 nM, 1 nM, 10 nM, 100 nM, 1 μM, 10 μM, respectively. Lane 8 shows translation in the presence of control morpholino oligo at the concentration of 10 μM. Wise translation is partially blocked at concentration of 1 μM, and completely blocked at 10 μM.

When the morpholino oligo was injected into the whole embryo at the 1 cell stage, embryos developed cyclopic eyes (Figs. 5L-5N), and the trunk and tail were shortened in most cases (Figs. 5F and 5L). At later stages, morpholino-injected embryos showed defects in eye formation (Fig. 5I), which were rescued by co-injection of Wise RNA (Fig. 5K). Fig. 5K shows the rescue of the eye defect resulting from injection of the morpholino oligos by co-injection of Wise RNA.

Figs. 5L-5N are the phenotypes of embryos following injection of Wise morpholino oligos throughout the whole embryo. Fig. 5L shows the range of cyclopic eye and short trunk phenotypes induced by the oligos in comparison to the control embryo (left). Section of control (Fig. 5M) and morpholino-injected (Fig. 5N) embryos at the level of eye are shown. In the Wise morpholino-injected embryos, eyes are positioned very close to the neural tube.

These results suggest that the endogenous role of Wise is to mediate elongation of the trunk, morphogenesis of the ectoderm/neuroectoderm, and formation of the eye. The fact that both ectopic expression of Wise, and inhibiting its function by injection of the antisense morpholino oligo resulted in similar defects in eye formation, suggests that this process requires a precise level of signaling, mediated by Wise.

Example 7.

The present Example relates to the immunoprecipitation procedures previously discussed. To test protein secretion, RNA encoding the HA tagged version of Wise was synthesized and injected into *Xenopus* oocytes. This HA tagged Wise construct was confirmed to be functional by testing its ability to induce En2 in Noggin-injected animal caps. Fifteen oocytes were incubated in 96-well dish with 150 μl of OR2 medium + 0.01% BSA for 2 days. Oocytes and the conditioned medium were collected separately and used for Western blotting with an anti-HA antibody (Boehringer). This construct was also transfected into COS cells and assayed for secretion by Western blotting.

For protein interaction studies, COS cells were transfected with DNA constructs encoding tagged versions of the proteins. Cells were harvested and proteins were extracted in 150 mM NaCl, 1% NP40, 0.5% Sodium Deoxycholate, 0.1% SDS, 50mM Tris-HCl (pH8), a cocktail of protease inhibitors (Complete, Boehringer), and 1 mM AEBSF at 4° C. Small aliquots were kept as cell extracts for checking expression of each protein. Primary antibodies against the epitope and Protein A-coupled beads were added to the extracts, incubated for 2 hours, and collected by centrifugation. Following several rounds of washing, pellets were re-suspended in loading buffer in the presence of SDS and subjected to electrophoresis and Western

blotting. The proteins were detected by using the epitope-specific antibodies and appropriate secondary antibodies conjugated to alkaline phosphatase.

Example 8.

The ability of Wise to interact with the Wnt pathway, and the fact that it is normally expressed in a transient manner in the non-neural surface ectoderm, suggest that it might have a role in modulating Wnt signaling in this tissue (Fig. 3). A balance between Wnt and BMP signaling in the surface ectoderm and dorsal neural tube is important in modulating dorsal fates and the generation of neural crest cells. Furthermore, Wnts in the surface ectoderm influence patterning of the underlying somites and their derivatives. The distribution and timing of Wise expression in the surface ectoderm, together with the result of morpholino experiments, suggest that it promotes precise levels of Wnt signaling to control some of these interactions.

Figs. 6A-6C show RT-PCR of Noggin treated animal caps assayed for En2 (en) induction. NCAM is used as a pan neural marker and Efl a is a loading control. Fig. 6A shows the induction of En2 by Wnt8 or Wise RNA is blocked by dominant-negative (dn) Frizzled 8 (ΔFz8). Noggin was added in an amount equal to (500 pg); Wnt8 was (50 pg); Wise was (1.2 ng); and ΔFz8 (2 ng). In Fig. 6B, the following constituents were added: Noggin (500 pg); Wise (600 pg); ΔWnt8 (200 pg); ΔDsh(dd1) (1.2 ng); GSK3 (500 pg); and LEFΔN (200 pg). Fig. 6B shows the induction of En2 is blocked by dn-Wnt8 (ΔWnt8), dn-dishevelled (ΔDsh(dd1)), GSK3 and dn-Lefl (LEFΔN). Fig. 6C shows the induction of En2 requires signaling components of the canonical Wnt pathway but not the planar cell polarity (PCP) pathway. Wise-mediated En2 induction was abolished by ΔDsh(dd1), a dominant negative form of Dishevelled for both pathways, and ΔDsh(DIX), which blocks the canonical pathway. ΔDsh(DEP) blocks the PCP

pathway but has no effect on Wise induction of En2. ΔDsh(ΔN) specifically activates the PCP pathway but fails to induce En2 in the absence of Wise, although full length d

Dishevelled (Dsh) is able to do so. In Fig. 6C, the following constituents were added: Noggin (500 pg); Wise (1.2 ng); Dsh (1 ng); and ΔDsh(d1), ΔDsh(DIX) and ΔDsh(DEP) (2.0 ng). Figs. 6D-6G: TCF3 (300 pg); Wnt8 (25 pg); Wise (300 pg); and β-catenin (100 pg) were added in the listed amounts.

Figs. 6D-6G show staining for sub-cellular localization of endogenous β-catenin detected immunocytochemically in *Xenopus* animal caps following RNA injection of: D, TCF3; E, Wnt8+TCF3; F, Wise+TCF3; and G, β-catenin+TCF3. Wnt8 (E) and Wise (F) promoted accumulation of nuclear β-catenin.

Wise activated the Wnt signaling pathway in animal caps. Since Wnts and Wise both induced En2 expression in Noggin-injected animal caps, whether Wise required Wnt signaling for its activity was investigated. To test, Wise RNA was co-injected with either wild-type GSK3β or dominant negative (dn) versions of the canonical Wnt pathway components, Wnt8, Frizzled, Dishevelled or Lef1. All of these Wnt blocking reagents eliminated the ability of Wise to induce En2 in neuralized animal caps (Figs. 6A and 6B). The finding that dn-Wnt8 and dn-Frizzled8 blocked Wise activity implied that it may use the same receptor(s) as Wnt. With respect to the intracellular components, Dishevelled (Dsh) is an important branch point in Wnt signaling that separates the canonical nuclear pathway from a planar cell polarity (PCP) pathway. Different truncated dishevelled constructs were used to examine the roles of the different pathways in En2 induction. Both ΔDsh (dd1), which lacks a part of the PDZ domain necessary for both the canonical pathway and the PCP pathway, and ΔDsh (DIX), which is a specific dominant negative form for the canonical pathway, abolished En2 induction by Wise (Figs. 6B

and 6C). In contrast, both ΔDsh(DEP), which specifically blocks the PCP pathway, and ΔDsh (ΔN) which constitutively activates the PCP pathway, had no effect on En2 induction (Fig. 6C). These results suggested that the domains of Dsh, critical for the canonical Wnt signaling pathway, are essential for Wise function.

Example 9.

This Example demonstrates that expression of Wise interferes with Wnt signaling. Although induction of En2 can be explained in terms of activation of Wnt signaling, the effects of injected Wise RNA on cement gland formation (Fig. 5B) resemble those seen when the Wnt pathway is inhibited. Therefore, it is possible that Wise also inhibits Wnt signaling. As such, Wise's ability to antagonize Wnt8 activity in axial induction was examined.

In particular, Figs. 7A-7C show the secondary axes induced by Wnt8 are blocked by Wise. Injection of Wnt8 RNA into a ventral vegetal blastomere of 4-8-cell stage embryos induced complete secondary axis formation (Fig. 7A). Co-injecting Wise blocked formation of Wnt8-induced secondary axis (Fig. 7B), similar to co-injection of a dominant negative Dishevelled, ΔDsh(DIX) (Fig. 7C).

Figs. 7A-7C show Wnt8 (5 pg); Wise (200 pg); and ΔDsh(DIX) (1 ng) that were added in the listed amounts. In Fig. 7D Wise (1 ng); Wnt8 (100 pg); Dsh (1 ng); and β-catenin (200 pg) were added in the listed amounts.

When Wnt8 RNA was injected into a ventral vegetal blastomere at 4-8 cell stages, it induced an ectopic secondary axis. Co-injection of Wise RNA completely blocked Wnt8-induced secondary axis. This inhibition was comparable to that mediated by a dominant negative form of Dsh (Fig. 7C).

Fig. 7D shows that Wise functions extracellularly to block induction of Siamois and Xnr3 by the Wnt pathway in ventral marginal zones. Wise blocks the ability of Wnt8 to induce Siamois and Xnr3, but it does not interfere with the ability of Dishevelled (Dsh) or β-catenin (β-cat) to induce these markers.

This inhibitory activity was examined at the molecular level in ventral marginal zone explants by assaying for Wnt-dependent induction of Xnr3 and Siamois, two immediate early response genes. In agreement with the axial duplication assays, the induction of Xnr3 and Siamois in ventral marginal zones by Wnt8 was blocked by the co-injection of Wise (Fig. 7D). However, Wise had no effect on the ability of injected intracellular components, such as Dishevelled and β-catenin to induce Xnr3 and Siamois (Fig. 7D). This suggests that Wise functions extracellularly to interfere with canonical Wnt signaling.

Example 10.

The inhibitory effect of Wise on the Wnt pathway was further examined by assaying secondary head induction dependent upon simultaneously blocking both BMP and Wnt signaling. When BMP signaling is blocked at the ventral marginal zone by a truncated BMP receptor (tBR), an incomplete secondary axis is formed (Fig. 7E). However, simultaneous inhibition of both BMP and Wnt signaling resulted in the formation of a complete secondary axis with eyes and cement glands. Co-injection of tBR and Wise induced a complete secondary axis (Fig. 7F), demonstrating that Wise blocked the Wnt pathway in this context.

Wise affected planar cell polarity. While the activation and inhibition properties of Wise in animal caps and embryos, described above, are dependent upon the canonical Wnt pathway, it is possible that Wise also influences the PCP pathway that branches at Dishevelled. Wnt11 is required for proper convergent extension movements of mesoderm during gastrulation in frogs

and fish, and this has been shown to be dependent upon the PCP pathway of Wnt signaling. Animal caps cultured in the presence of Activin form mesoderm and undergo convergent extension movements, which can be blocked by reagents that either elevate or decrease Wnt signaling. This implies that precise levels of Wnt signaling through the PCP pathway are essential for coordinated cell movements. Figs. 7E and 7F show that Wise acted as Wnt inhibitor and induced head attribute formation in an incomplete secondary axis system. When BMP signaling was blocked at the ventral marginal zone by injection of a truncated BMP receptor (tBR), an incomplete secondary axis was formed (Fig. 7E). Co-injection of tBR and Wise induced a complete secondary axis with eyes (arrows) and cement gland (Fig. 7F).

Figs. 7G-7I show how Wise blocks cell movements in Activin-treated animal caps. Control animal caps (Fig. 7G) undergo gastrulation-like movements in the presence of Activin (Fig. 7H). In Wise injected animal caps, elongation was blocked (Fig. 7I), but mesoderm induction occurred. In this animal cap assay, injection of Wise RNA blocked cell movements preventing elongation of animal caps, but had no effect on Activin-induced mesoderm formation (Figs. 7G-7I). This suggested that Wise influenced the Wnt-dependent PCP pathway, but whether activation or inhibition of the pathway resulted, cannot be distinguished. This effect on cell behavior in animal caps is consistent with and may explain the phenotypic effects observed in Wise-injected whole embryos. Wise perturbed the morphogenesis of the neural tube, which failed to close. It was thickened and shorter, and there was a lateral expansion and broadening of A-P markers. Many of these defects appear related to abnormal convergent extension movements during gastrulation. However, the fact that morpholino antisense oligo does not interfere the neural A-P markers (Fig. 4), and that Wise is not predominantly expressed at gastrula state (Fig. 2), both suggest that endogenous Wise is unlikely to be involved in

gastrulation movement. Instead, Wise has a potential to interfere with the Wnt-mediated PCP pathway.

Example 11.

The mechanisms of action were investigated as potential physical interactions of Wise, with Wnt family members or their putative co-receptors Frizzled (Hsieh et al., 1999) and LRP6 (Tamai et al., 2000) or Frizzled8 (Hsieh et al., 1999) with Wise conditioned medium, and assayed for interactions by immunoprecipitation (IP). In this assay, Wise bound to LRP6 and Frizzled 8, but not to Wnt8 (Fig. 8). Recent studies have shown that individual members of the Dickkopf (Dkk) family of secreted proteins can either antagonize or stimulate Wnt signaling through interaction with LRP6 (Brott and Sokol, 2002; Mao et al., 2001; Wu et al., 2000). Therefore, IP experiments were performed to determine if Wise shared common binding sites with Dkk1 or Wnt on LRP6. The extracellular domain of LRP6 contains four EGF repeats and Dkk1 interacts with repeats 3-4, while Wnt interactions seem to involve repeats 1-2 (Mao et al., 2001). It was found that Wise binds to LRP6 and a variant where EGF repeats 3 and 4 are deleted (ΔE3-4), but not to one in which EGF repeats 1 and 2 are removed (ΔE1-2)(Fig. 8A). Conversely, Dkk1 binds to LRP and ΔE1-2, but not to ΔE3-4 (Fig. 8A). These results showed that Wise shared the domain on LRP6 essential for interaction with Wnt and that Wise and Dkk1 modulate LRP6 activity by interacting through different domains. Wise and Wnt8 were tested to determine whether they could bind to LRP6 at the same time, or whether they compete for binding. As shown in Fig. 8C, Wise interferes with the binding of Wnt8 to LRP6. This suggested a mechanism, whereby Wise inhibits Wnt signaling by competing with Wnt8 for binding to LRP6 (Fig. 8D).

In conclusion, the results demonstrate that Wise influenced both the canonical and PCP pathways of the LRP/Wnt signaling cascade. The novel ability to both activate and inhibit Wnt signaling through actions of a single discrete regulatory molecule, places Wise in a unique position as a modulator of Wnt signaling.

Example 12.

In this Example, Sost inhibition of the Wnt pathway is described. It has been demonstrated that Wise acts to inhibit the Wnt pathway. The functional inhibition of Wnt was shown to be derived from the second exon of Wise, which encodes the cysteine knot. Since the cysteine knot of Sost is 70% homologous to that of Wise (Fig. 9), thus Sost's potential functioning in a similar fashion was explored. Sost RNA was either microinjected alone or in combination with other factors into *Xenopus* embryos and dorsal marginal zones were assayed for early immediate Wnt response genes, Siamois and Xnr3 (Fig. 11). It was found that, like Wise, Sost was able to inhibit the action of Wnt on Siamois and Xnr3 (Fig. 11). This Wnt inhibition by Sost was found to be working upstream from β-Catenin (Fig. 11). Like Wise, Sost was able to rescue secondary axis formation by Wnt (Fig. 11). However, unlike Wise, Sost was unable to completely restore a normal axis (Fig. 11).

Wise has also been shown to induce En2 at a distance in *Xenopus* Noggin animal cap assays. En2 expression at a distance is from an induction of Wnt gene activity. The conclusion was that Wise had induced, at a distance, more posterior neural markers in an anterior neuralized animal cap. Next it was analyzed whether Sost and Wise could be redundant by looking to see if Sost could also induce En2, like Wise. *Xenopus* embryos were either injected with Noggin and/or with Sost or Wise. We found that Wise injected animal caps induced En2 expression, however

Sost injected caps did not (Fig. 11). This unexpected finding led to further examination of these two genes.

Example 13.

A Wise knockout mouse was made as detailed herein. A Neo-lacZ cassette, containing stop codons at the 3' end, was inserted into a Wise gDNA sequence isolated bacterial artificial chromosome (BAC) from a 129 strain of mouse by conventional cloning techniques. The mouse Wise DNA sequence is SEQ ID NO 1. A Sost knockout mouse can similarly be made. The mouse Sost sequence is SEQ ID NO 6. The Neo-lacZ cassette can be obtained from Stratagene (La Jolla, CA). The E. coli lacZ gene, when integrated into the mouse genome by standard cloning techniques, can be used as a reporter gene under the control of a given promoter/enhancer in a transgene expression cassette. The lacZ gene encodes β-galactosidase, which catalyzes the cleavage of lactose to form galactose and glucose. In the presence of X-gal chromogenic substrate, β-galactosidase converts the substrate into an insoluble blue dye, allowing identification of cells containing lacZ activity.

The 129 mouse strain, commonly utilized in creating "knockout" mice, was obtained from Jackson Laboratories, Bar Harbor, Maine. The Wise knockout mice produced lacked the presence of functional Wise polypeptide molecules. Sost knockout mice are predicted to lack functional Sost polypeptide molecules. Thus, these knockout mice may be referred to as functional mutants. In such mutant mice, protein translation is prematurely terminated.

A Neo-lacZ cassette, containing stop codons at the 3' end, was inserted into the first Exon of the Wise DNA, isolated BAC using the SmaI and EcoRI restriction sites. However, the Neo-lacZ cassette can also be inserted into a position within or adjacent to Exon 1 (SEQ ID NO 127) and Exon 2 (SEQ ID NO 128) of Wise. The Wise-containing BAC preparation was

exposed to cleavage enzymes, such as SpeI and BamHI, which yielded homologous arms containing 5' UTR and 3' intron nucleic acid sequences. These nucleic acid sequences permitted homologous recombination with wild type DNA from 129 mouse-derived embryonic stem (ES) cells upon introduction of the BACs into ES cells by the electroporation method described in Example 32. The Neo-lacZ cassette contained one or more stop codons terminating translation of Wise polypeptide, leading to production of a truncated Wise polypeptide, which lacked the cysteine knot motif. The Wise cysteine knot region is significant because this region (1) is homologous to cysteine knot regions of Sost and other family members as described herein, and (2) binds to LRP.

After recombination, the ES cells were grown in the presence of G148 for neomycin selection. Neo-lacZ cassette-containing ES cells were neomycin-resistant and positively selected. There were three possible event outcomes occurring when the resultant ES cells were cultured in neomycin-containing media: First, Wise Neo-lacZ cassette-containing ES cells grew, indicating a successful homologous recombination event within the first Exon region of Wise, as predicted. Second, no recombination occurred, resulting in the lack of the presence of a protective Neo-gene in the ES cells and cell death. Third, recombination occurred outside the first Exon of Wise, conferring neomycin resistance and ES cell survival and growth.

To distinguish between the above first and third categories of recombination events in live neomycin-resistant ES cell cultures, genomic DNA (gDNA) extracted from ES cells was divided into two aliquots. One part was frozen (-20 deg. C) for further investigation, and the other part was digested *in vitro* with EcoR I for Southern Blot analysis. By using a 3' probe within Wise Exon 2, EcoR I digestion yielded either a 6.8 Kb fragment associated with a homologous recombination event, or a 9.0 Kb fragment associated with a random integration

event. Frozen cultures from those plates that exhibited homologous recombination event were thawed, expanded and further processed for creation of Wise mutant mice by micro-injection of these Wise Neo-lacZ cassette-containing ES cells into blastomeres as described hereinafter.

In the process of electroporation of mouse ES cells, linearized Wise nucleic acid sequences containing the Neo-lacZ cassette were inserted into the nuclei of ES cells for incorporation into the host ES cell DNA. Similarly, Sost nucleic acid sequences with the Neo-lacZ cassette can be inserted into the nuclei of ES cells for incorporation into other host ES cell DNA. The electroporation process steps were as follows. ES cells were obtained from removed blastocysts obtained from mouse uteri and grown on mitotically inactivated Mouse Embryonic Fibroblast (MEF) feeder layers. An ES cell frozen ampoule was thawed and transferred to a sterile dish containing MEFs as a feeder layer at a concentration of 1 x 10^6 cells per 10 centimeter (cm) dish. ES cells were grown on the MEF feeder layer in ES media in T-150 flasks. ES cells were centrifuged and washed in transfection buffer (1 x Hebs). ES cells were then placed in a sterile "flat pack" 1.8 mm gap cuvette (BTX order #485), and the cuvette was inserted between the safety stand contacts.

The power was switched to the on position with the BTX 600 or equivalent electroporator set to 500V/capacitance and resistance, 500 uF capacitance timing, 360 ohms R8 resistance timing, and charging voltage 185V. After pipetting the ES cells up and down with a 5 ml pipette, targeting construct DNA (40 μg of clean linear DNA in 1 x TE @ 1 μg/μl for each electroporation) was added to the ES cells in a microfuge tube. Cells were pipetted up and down gently with a Pasteur pipette. Cells were slowly added to the cuvette which was then placed into the electroporation chamber. The start button was pushed, and electroporation occurred. After completion, electroporated ES cells were removed from the cuvette and placed in 5.0 ml of fresh

ES medium in a centrifuge tube. 2 ml of transfected ES cells were added to each dish containing inactivated MEF feeder layers. Dishes were rocked slowly to evenly disperse cells and incubated. ES cells were fed on day 9 and 12 with selection medium, and clones became visible as small nests under an inverted microscope. Clones were picked on day 13 or 14 using a pipettor set between 30 and 50 µl. Clones were each placed into one of 24 wells containing ES selection medium. On day 16 or 17, clones were frozen in ES freezing medium and stored at –70°C.

Each set of ES cells containing mutant Wise genes were injected into mouse embryos for creation of transgenic "knockout" mice. Such ES cells were microinjected into early mouse embryos (*i.e.*, blastocysts) which were then transferred to surrogate mothers for embryonic development. Targeted stem cells containing mutant Wise were placed in an injection chamber with expanded blastocysts. Stem cells were loaded into the injection needle and inserted into the blastocoel cavity of the recipient 129 or C57BL/6 embryo, then implanted into the uterus of a foster mother. Chimeric offspring were identified by coat color (*i.e.*, at 2 weeks) or other markers and confirmed by Southern blot analysis of tail biopsies (*i.e.*, at 3 weeks). Similarly, ES cells containing mutant Sost genes can be made and injected into ES cells to make Sost knockout mouse embryos.

The resulting pups (*i.e.*, chimeras) contained a (+) gene in some cells and a (-) gene in other cells. Chimeras were mated with normal mice. Pups were identified that carry one (+) and one (-) copy of the Wise gene, and these animals were mated with each other.

The mouse pups were then analyzed. About 25 percent of the pups were found to have inherited the (-) gene from both parents and completely lack the (+) or wild type gene. Homozygous (-) gene pups lacking the Wise wild type gene were termed "Wise knockout mice."

Similarly, homozygous (-) gene pups lacking the Sost wild type gene can be made, and these are referred to as "Sost knockout mice." Wise knockout mice were then utilized for subsequent experiments to determine effects relating to bone mineral density, bone deposition, embryo implantation, hair development, tooth abnormalities, ophthalmic abnormalities. Sost knockout mice may similarly be made and utilized in phenotypic experiments.

Example 14.

A Sost knockout mouse can be made using the procedure of Example 13 above. Briefly, a Neo-lacZ cassette, containing stop codons, can be inserted into a Sost gDNA isolated BAC from a 129 mouse strain by conventional cloning techniques. The Sost-containing BAC preparation can be electroporated and allowed to undergo homologous recombination into ES cells and be exposed to selection. ES cells containing mutant Sost can be injected into mouse embryos for creation of transgenic Sost knockout mice as previously described.

Example 15.

In this Example, the Wise knockout mice, produced in Example 12, were used to investigate the effect of the absence of a functional Wise polypeptide molecule upon opthalmic development. It was determined that ophthalmic abnormalities developed in these mutant mice. Immunodetection of Wise protein production in murine retinal regions was used to determine the efficacy of induced Wise mutation in the Wise mutant mice.

Polyclonal anti-Wise peptide antibody was prepared by rabbit immunization with Wise peptide antigens. Such antibodies were directed against the cysteine knot loop encoded by Exon 2 of Wise.

Zymed FITC-conjugated secondary polyclonal antibody directed against primary rabbit anti-Wise peptide antibody was also utilized in a histological sandwich immunoassay. Eye

mounts containing retinas or sections were stained with anti-Wise antibody and FITC-conjugated second antibody. In wild type mice, anti-Wise reactivity was detected as secreted Wise protein in the ganglion cell and optic fiber layers and in rods and cones. However, Wise mutant mice eyes lacked detectable anti-Wise peptide reactivity, indicating absence of Wise from tissues of these mutant mice.

The Wise mutant mice appeared to have lost the majority of the optic nerve fibers and had increased rod and cone layers in the retina (Fig. 12). These mice also exhibited abnormal retinal ganglion cells. Wise protein was found in the inner plexiform layer, ganglion cells and fibers, and in the rods and cone layer of a 2.5 month mouse retina (Fig. 12). Unlike Wise, Sost was found in the tissues adjacent to the neuroepithelium of the diencephalon at E18 dpc.

Example 16.

Wise mutants were analyzed to compare BMD in Wise mutants as compared to that in wild type mice. A Piximus instrument (Faxitron) was used to measure BMD, computed in whole mice by measurement of bone weight divided by area of bone measured.

The BMD in Wise mutants from the C57BL6 and 129 mouse strains was compared with that in wild type (wt) mice by the student t-test method. The resultant p value obtained for the BMD differences between C57BL6 vs. Wise mice was 0.0017. This indicates that BMD values increased in Wise mutant mice as compared to C57BL6 wt mice, with a significant difference between groups ($p < 0.01$) observed. Increased BMD values were also observed in the 129 Wise mutant mice in comparison with 129 wt mice.

Related to this finding, Fig. 13 shows results of bone staining and BMD measurements. Fig. 13A and 13C depict hematoxylin and eosin (H&E) staining of cross-sections of bone tissue from 16 to 18 days post cortum (DPC) mice. Fig. 13B and 13D show the same bone regions as

Figs. 13A and 13C; however, Fig. 13B shows staining with S-35 radiolabel attached to Sost RNA probes, wherein Sost is located in osteoblasts in 16 to 18 DPC mice. Fig. 13D also shows staining with anti-Wise peptide primary antibody and FITC-conjugated secondary antibody, and localization of Wise in hypertrophic and prehypertrophic proliferating chondrocytes.

Fig. 13E and 13F show graphical depictions of bone density measurements and total bone weight measurements, respectively. Fig. 13E shows that observable significant differences in BMD measurements between Wise mutant and wild type mice occur at ages between 0 and 3 months. Wise mutant bone is higher in density than wt bone in this age range. At 4 months, there appears to be no significant difference between mutant and wt groups. Fig. 13F depicts total bone weight measurements. Note that at 2.5 months wt bone weight is 19.87, significantly different from the Wise bone weight of 24.67. Therefore, some of the increase in BMD found at 2.5 months can be attributed to increase bone weight and not necessarily an increased BMD. Consistent with data in Figs. 5E and 5F, it is concluded that during the 0 to 3 month period, bone deposition occurs. However, at the 4 month maturation stage, it is postulated that regulatory genes are switched on to remodel bone deposition and bone removal, wherein osteoclasts may be triggered to remove previously deposited bone.

In summary, one tissue cell type that both Sost and Wise genes appear to affect in a similar fashion is the bone. Sost is expressed in osteoblasts. Sost may also be expressed in osteoclasts. In contrast, Wise is expressed in periosteum, and its protein is found on chondrocytes (proliferating, prehypertrophic and hypertrophic), but not in the growth plate (Fig. 5). Yet, both Sost and Wise genes display a similar phenotype of increased bone density, albeit potentially activated at different developmental stages. As such, Wise mutant mice have increased bone density during early prenatal bone development (under 4 months), and cease to

exhibit increased bone density once bone-modeling begins (4 months; Fig. 5). However, Sost mutations result in increased bone density during the subsequence developmental stage in which the adult bone remodeling process occurs.

Example 17.

Genetic regulation in tooth and jaw development was examined in wild type and Wise mutant mice as shown in Fig. 14. The mice were dissected, and the jaws were placed in a proteinase K solution (2x SSC, 0.2% SDS, 10mM EDTA, and 100ul of 10mg/ml proteinase K) overnight at 55°C. The next day the jaws were air-dried. A digital Faxitron was used for capturing X-ray images of the mouse jaw. The teeth were removed using tweezers.

Figs. 14A, 14D, and 14G show hematoxylin and eosin staining of a jaw cross-section. Figs. 14B, 14E, and 14H show S-35 RNA probe-labeled Sost staining. Figs. 14C, 14F, and 14I show S-35 RNA probe-labeled Wise staining. Generally, these figures show that Sost appears in ondontoblasts and osteoblasts. In contrast, Wise is found in incisors, dental follicles, and hair follicles in the whisker pad.

The top sectional Figs. 14A,14B, and 14C show a bilateral view of two molars with developing tooth buds. Fig. 14C shows that Wise labels layers of the dental follicle of molar teeth.

The middle sectional Figs. 14D, 14E, and 14F show a molar tooth bud at a higher magnification. Fig. 14E shows Sost staining in osteoblasts of the trabecular bone adjacent to the molar tooth. Visible staining of the odontoblasts occurs along the base of each molar. Fig. 14F shows Wise staining of dental follicle layers.

The bottom sectional Figs. 14G, 14H, and 14I show incisor tooth staining patterns. Fig. 14G shows the morphological features of two incisors, with the nasal cleft between them,

tongue, and hair follicles of the whisker pad. Fig. 14H shows Sost staining in osteoblasts of trabecular bone. Fig. 14I shows prominent Wise staining of incisors. Hair follicles and the whisker pad are also stained with Wise labeled RNA probes.

Figs. 14J and 14K show X-ray photographs of incisor teeth in the maxilla (upper jaw) regions of the wild type and Wise mutant mice, respectively, utilizing a 129 strain genetic background. The Wise mutant jaw, shown in Fig. 14K, possesses an additional incisor tooth (i') not present in the wt mouse shown in Fig. 14J. The additional tooth may originate from either an additional tooth bud or, alternatively, from a bifurcation of the original incisor.

Figs. 14L, 14M, 14N, and 14O show the patterning in molar teeth observed in wt (Figs. 14L and 14N) as compared to Wise mutant mice (Figs. 14M and 14O), against a C57BL6 genetic background (Figs. 14L and 14M) and 129 background (Figs. 14N and 14O). Fig. M shows an additional M1 molar in the Wise mutant mouse in comparison to the M1, M2, and M3 molars present in the wt mouse in Fig. 14L. Fig. 14O shows tooth abnormalities in the Wise mutant mouse. The M1 and M2 molar teeth are fused together. Moreover, there is a reversal of the order of molar bone patterning, wherein an M3/M2-1 pattern appears in the Wise mutant, in contrast to the wild type's M1/M2/M3 pattern. Occasionally, an additional M4 molar tooth appears in the Wise mutant.

It was observed that Wise mutant mice possessed tooth abnormalities. The incisors occurred in duplicate number in comparison with wt mice, and these teeth required weekly clipping from the weaning stage onwards. In addition, the molars also displayed abnormal patterning. The three molars were often found in reverse orientation and also showed fusion of M1 and M2. In contrast to Wise mice, Sost human mutations did not display these molar and incisor tooth phenotypic abnormalities, probably because of the differences in Sost and Wise

gene expression distributions in bone. Thus, Sost was expressed in the polarized odontoblasts and the surrounding osteoblasts. Wise, on the other hand, is expressed in the dental follicle surrounding the tooth bud and in the incisors. Thus, Sost and Wise were expressed in complementary cell types, wherein differing tooth and eye phenotypic expression patterns are anticipated and observed in Sost human mutations and Wise mutants.

Example 18.

Plasmid vectors containing Wise nucleic acid sequences were prepared for the purpose of producing Wise proteins and polypeptides. Sost vectors were similarly prepared for the purpose of producing Sost proteins and polypeptides. The expression vector, pET-28b (Novagen pET System Manual), was used for the expression of Wise and Sost, LRP5 and LRP6 sequences. This plasmid utilizes the phage T7φ10 gene promotor. This promotor is not recognized by E. coli DNA dependent RNA polymerase, and thus will not produce substantial levels of the polypeptide unless T7 RNA polymerase is present. Strain BL21 (DE3) contains a lysogenic λ phage that encodes the required polymerase under control of the lacUV5 promotor. A recombinant protein that was made was the intact Wise, Sost, LRP5 or LRP6 proteins. The Wise pET vector which was created by placing an EcoRI-HindIII fragment containing chick Wise cDNA into the pET28B vector which was then digested with EcoRI-HindIII. Extra amino acids 5' to Wise Start, ATG were removed, along with extra amino acids 3' to the Wise stop codon. The Sost pET vector was created by placing a BamHI-XhoI fragment containing mouse Sost cDNA into pET BamHI-XhoI. The amino acids from the 5' and 3' ends to the Sost coding region were removed using mutagenesis. The 3' amino acids were deleted and the missing ELENAY was inserted at the 3' end.

Example 19.

In this Example, the method used for protein production for Wise, Sost, LRP5, and LRP6 polypeptides in HEK293 mammalian cells is outlined briefly. PCS2+ Sost-FLAG, PCS2+ Wise-FLAG, or PCS2+ LRP6 IgG, PCS2+LRP5-Myc DNA was transfected into the HEK293 cells using FuGENE 6 Transfection Reagent (10 μg DNA/100 mm plate) (Roche Diagnostics Corp., Indianapolis, IN). The FuGENE reagent is a multi-component lipid-based tranfection reagent that complexes with and transports DNA into the cell during transfection. Adherent cells were plated one day before transfection, and freshly passaged HEK293 suspension cells were prepared. FuGENE 6 reagent:DNA ratios of 3:2, 3:1 and 6:1 were used to transfect HEK293 suspension cells.

After incubation, cell supernatants, containing the polypeptide of interest (Wise, Sost, LRP5, LRP6), were collected on days 1, 2, 3, and 4. Polypeptide-containing supernatants were concentrated by Amicon Ultra-15 column passage (20 ml to 500 μl). Some aliquots were frozen, and other aliquots were used in Western blot and immunoprecipitation quantitation and characterizations using standard methodologies. Mixtures of Wise and LRP5, Wise and LRP6, Sost and LRP5, and Sost and LRP6 were analyzed for binding by immunoprecipitation and Western blot analysis. See SuperSignal West Dura Western Blotting Kit (Pierce, Rockford, IL), Trans-Blot SD Semi-Dry Electrophoretic Transfer and Mini-PROTEAN 3 Electrophoresis (Bio-Rad Labs., Richmond, CA), Hybond – P PVDF Membrane for protein transfer (Amersham Pharmacia Biotech), Chroma Spin Columns (Clontech, Palo Alto, CA).

Immunoprecipitation was performed with anti-Wise antibody, anti-Myc, anti-Flag, and protein G sepharose (Sigma, St. Louis, MO) or protein A sepharose (Repligen). Briefly, transfected cell supernatents were prepared and 1-3 μg of antibody added. After incubation, 30

μl of protein G sepharose was added, incubated, and beads were centrifuged. Beads, containing antibody from supernatents as the immunoprecipitate, were washed in buffer, then submitted to SDS-PAGE analysis and Western Blot analysis. Alternatively, immobilized antibody was used in immunoprecipitation of proteins.

In Western Blots, electrophoresis was performed upon the cell supernatent material above. After wash, water rinse, and equilibration of the PVDF membrane in transfer buffer, papers were sandwiched as follows: pre-soaked thick paper, membrane, gel, pre-soaked thick paper. Power was turned to 10V to 15V for 30 min. After transfer of protein to the HyBond-P PVDF membrane, the membrane was incubated in blocking buffer, rinsed, and incubated with antibody solution. After wash, a secondary antibody was added, washed, then ECL-plus added. After exposure of X-ray film, patterns were read. As such, protein production in PCS2+ transfected HEK293 cells was performed to support purification and characterization of Wise, Sost, LRP5, and LRP6 polypeptides.

Example 20.

A method for the production of large quantities of Wise and Sost polypeptides is described. Bacteria cells transfected with either the Wise or Sost genes can be grown. E. coli strain DME558 is grown on LB agar plates at 37°C.

For P1 transduction, a P1 viral lysate of the E. coli strain DME558 is used to transduce a tetracycline resistance marker to strain BRE51 (Bremer, E., et al., FEMS Microbiol. Lett. 33:173-178 (1986)) in which the entire OmpA gene is deleted (Silhavy, T. J., et al., Experiments with Gene Fusions, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1984)). Strain DME558, containing the tetracycline resistance marker in close proximity of the OmpA gene, is grown in LB medium until it reached a density of approximately 0.6 OD at 600 nm. One tenth of

a milliliter of 0.5 M $CaCl_2$ is added to the 10 ml culture and 0.1 ml of a solution containing $1x10^9$ PFU of $P1_{vir}$.

The culture is incubated for 3 hours at 37° C. After this time, the bacterial cell density is visibly reduced. 0.5 ml of chloroform is added and the phage culture is stored at 4° C. Because typically 1-2% of the E. coli chromosome can be packaged in each phage, the number of phage generated covers the entire bacterial host chromosome, including the tetracycline resistance marker close to the OmpA gene.

Next, strain BRE51, which lacks the OmpA gene, can be grown in LB medium overnight at 37° C. The overnight culture is diluted 1:50 into fresh LB and grown for 2 hr. The cells are removed by centrifugation and resuspended in MC salts. 0.1 ml of the bacterial cells are mixed with 0.05 of the phage lysate described above and incubated for 20 min. at room temperature. Thereafter, an equal volume of 1 M sodium citrate is added and the bacterial cells are plated out onto LB plates containing 12.5 μg/ml of tetracycline. The plates are incubated overnight at 37° C. Tetracycline resistant (12 μg/ml) transductants are screened for lack of OmpA protein expression by SDS-PAGE and Western Blot analysis, as described below. The bacteria resistant to the antibiotic possess the tetracycline resistance gene integrated into the chromosome very near where the OmpA gene had been deleted from this strain. One particular strain was designated BRE-T^R.

A second round of phage production can be then carried out with the strain BRE-T^R, using the same method as described above. Representatives of this phage population contain both the tetracycline resistance gene and the OmpA deletion. These phage are then collected and stored. These phage are used to infect E. coli BL21(DE3). After infection, the bacteria contain

the tetracycline resistance marker. In addition, there is a high probability that the OmpA deletion is selected on the LB plates containing tetracycline.

Colonies of bacteria obtained from plates are grown up separately in LB medium and tested for the presence of the Wise and Sost protein and OmpA protein as judged by antibody reactivity on SDS-PAGE western blots.

The SDS-PAGE is a variation of Laemmli's method (Laemmli, U. K., Nature 227:680-685 (1970)) as described previously (Blake and Gotschlich, J. Exp. Med. 159:452-462 (1984)). Electrophoretic transfer to Immobilon P (Millipore Corp. Bedford, Mass.) is performed according to the methods of Towbin et al. (Towbin, H., et al., Proc. Natl. Acad. Sci. USA 76:4350-4354 (1979)) with the exception that the paper is first wetted in methanol. The Western blots are probed with phosphatase conjugated reagents (Blake, M. S., et al., Analyt. Biochem. 136:175-179 (1984)).

Example 21.

The fusion constructs of Example 18 can be used to transform the expression strain BL21 (DE3) ΔOmpA of Example 19. The transformation plates are cultured at 30°C. Colonies of both types are isolated from these plates and analyzed. It is generally found that virtually all transformants contained the desired plasmid DNA.

Various fusion-Wise clones are then analyzed for protein expression. The clones are induced and grown in LB media containing 0.4% glucose and 118 μM carbenicillin instead of ampicillin with an aeration speed of 100 to 150 rpm and at about 30°C. The expression of the Wise protein is analyzed by loading 0.1 ml of the culture of total E. coli proteins on an 8-16% gradient SDS gel.

E. coli strain BL21 (DE3) ΔOmpA [pNV-3] can be grown to mid-log phase (OD=0.6 at 600 nm) in Luria broth. Isopropyl thiogalactoside is then added (0.4 mM final) and the cells were grown an additional three hours at 30°C. The cells are then harvested and washed with several volumes of TEN buffer (50 mM Tris-HCl, 0.2 M NaCl, 10 mM EDTA, pH=8.0) and the cell paste stored frozen at -75°C.

For purification, about 3 grams of cells are thawed and suspended in 9 ml of TEN buffer. Lysozyme was added (Sigma, 0.25 mg/ml) deoxycholate (Sigma, 1.3 mg/ml) plus PMSF (Sigma, 10 μg/ml) and the mixture was gently shaken for one hour at room temperature. During this time, the cells lyse and release DNA causing the solution to become viscous. DNase is then added (Sigma, 2 μg/ml) and the solution again mixed for one hour at room temperature. The mixture is then centrifuged at 15 K rpm in an SA-600 rotor for 30 minutes and the supernatant discarded. The pellet is twice suspended in 10 ml of TEN buffer and the supernatants discarded. The pellet is suspended in 10 ml of 8 M urea (Pierce) in TEN buffer.

Alternatively, the pellet can be suspended in 10 ml of 6 M guanidine HCl (Sigma) in TEN buffer. The mixture is gently stirred to break up any clumps. The suspension is sonicated for 20 minutes or until an even suspension is achieved. 10 ml of a 10% aqueous solution of 3,14-ZWITTERGENT is added and the solution is thoroughly mixed. The solution is again sonicated for 10 minutes. Any residual insoluble material is removed by centrifugation.

This mixture is then applied to a 180.times.2.5 centimeter (cm) column of Sephacryl-300 (Pharmacia) equilibrated in 100 mM Tris-HCl, 1 M NaCl, 10 mM EDTA, 20 mM $CaCl_2$, 0.05% 3,14-ZWITTERGENT, pH=8.0. The flow rate is maintained at 1 ml/min. Fractions of 10 ml are collected. Three dimensional conformation was restored in Wise during the gel filtration. The absorbance (OD = 280 nm) of each fraction is measured and those fractions containing protein

are subjected to SDS gel electrophoresis assay for Wise. Those fractions containing Wise are pooled and stored at 4°C for 3 weeks. During the incubation at 4°C, a slow conformational change occurs. The Wise protein remained in solution without the elevated levels of salt. The pooled fractions are then dialyzed against 50 mM Tris-HCl, 200 mM NaCl, 10 mM EDTA, 0.05% 3,14-ZWITTERGENT, pH = 8.0. This material is applied to a 2.5x cm Fast Flow Q Pharmacia column equilibrated in the same buffer. Any unbound protein is eluted with starting buffer. A linear 0.2 to 2.0 M NaCl gradient is then applied to the column. The Wise elution profile can be characterized. Fractions are assayed by SDS-PAGE and the purest fractions pooled and dialyzed against TEN buffer containing 0.05% 3,14-ZWITTERGENT. Thus, cells transfected with the constructs can be isolated for Wise protein production. Similarly, Sost transfected cells can be isolated for Sost protein production.

Example 22.

The family tree associations of relatedness between Sost, Wise, and other cysteine knot proteins were analyzed. Sost and Wise cysteine knot protein sequences were analyzed using BLAST, and all significant sequences were isolated. The cysteine knots from all sequences were aligned using the software T-Coffee and then analyzed with Phylip bootstrap neighbor joining methods. To determine chromosomal locations, Wise and Sost DNA sequences were compared against sequences in the mouse and Ensembl database (http://www.ensembl.org/Mus_musculus/blastview).

The BLAST program optionally filters out low-complexity regions from the search and assigns scores with well-defined statistical interpretation such that real matches of related sequences can be distinguished from random background hits. The default scoring matrix is BLOSUM62. The significance of each of the matches is given an Expect (E) score, defined as

the expected number of alignments between a random query sequence and a database of random sequences of the same "effective" length and number that will score as well.

A Wise cDNA, (SEQ ID NO 1) was isolated and submitted to NCBI for BLAST sequencing. The Wise cDNA was comprised of 618 nucleic acids, corresponding to 206 amino acids in the wild type polypeptide molecule. 743,070 sequences were searched in the database. From this search, it was determined that Wise and Sost were related. Both genes had two exons and an intron. Exon 2 for both genes was 400 bp long and possessed two cysteine domains that were 70% identical.

Fig. 9D shows the family tree relatedness between cysteine knot protein members Sost and Wise. In initial experiments, when the BLAST analysis was performed for Wise protein alone, only CCN family members (*e.g.*, Slit, Mucin) were obtained as related family members. When Sost alone was run, only DAN family members (*e.g.*, Caronte, Gremlin) were determined to be related. However, when Sost and Wise BLAST analyses were performed together, the family tree was that depicted in Fig. 9D. In this analysis of cysteine knot protein relatedness, it was noted that the DAN family had only one cysteine knot motif. In contrast, the CCN family and Slit and Mucin family possessed ten different protein motifs. Other family proteins had an additional cysteine knot moiety. G and P are conserved.

In Fig. 9D, the red dots indicate significant relatedness among cysteine knot proteins. Thus, Fig. 9D depicts the following family branch associations, wherein Sost and Wise are present in one branch. Nov, CTGF, Cyr61, and Cef10 are present in one closely related branch to Sost and Wise. Cerberus, Caronte, and Gremlin are in a second closely related branch. The aforementioned three branches are more remotely related to the following branches: the Muc2, Apomucpig, and Muc58 branch; the VWF branch, and the Slit 1, Slit2, Slit3, Muc5AC, and

Gastmuc branch. Numerical values in the tree in Fig. 9D indicate a measure of the significance of protein associations. The closer a number is to 100, the more significant the association. Numerical values of less than 50 indicates insignificant associations. Thus, the numerical value of 97 between Sost and Wise is highly significant.

Example 23.

An *in situ* protocol for detection of gene expression in Sost mutant mice was conducted. 3' untranslated regions of the Sost gene were obtained.

DNA from these 3' translated gene regions were linearized from the vector, then clipped at the 5' end. Subsequently, this sequence was transcribed to produce an antisense RNA molecule. The antisense RNA molecule was labeled with a deoxygenin (DIG) substrate tag. The DIG-labeled RNA was then utilized to bind to an embryo's RNA.

In preparation for staining, a whole embryo was dehydrated and then bleached at the pigment stage. The next day, the embryo was washed and treated with detergent to induce permeability in subsequent staining. When the DIG-labeled RNA was incubated with RNA from an embryo, a purple-blue color was developed in whole embryo staining in the presence of alkaline phosphatase, NBT and BCIP. Using this procedure, Sost expression in whole embryo tissue was characterized.

Example 24.

A chick Wise pET28b vector was made. The Novagen pET28b(+) vectors used contained f1 origin, N-terminal histidine, T7, and optional C-terminal histidine tags. Single-stranded sequencing was performed using the T7 terminator primer. An EcoR I-HinD III nucleic acid fragment was obtained from a chick Wise-containing pcDNA3.1-Myc-His vector for

insertion into the pET28b vector by established Novagen methods (Novagen, Madison, WI) described in various pET28b examples herein.

Example 25.

A mouse Sost pET28b vector was made. A Sost-V5 epitope-tagged version was utilized as a base construct for making the pET28b(+) construct. Subsequently, Sost was removed from the base construct using BamHI and XhoI enzymes and inserted into pET28b vectors according to Novagen methods as previously described. The Sost-containing preparation was expanded using the PCR method. Nucleic acids encoding thirteen excess amino acids were removed 5' from the start codon of the Sost nucleic acid sequence utilizing the Stratagene site-directed mutagenesis kit. Also removed were extra restriction enzyme sites adjacent to Xho or located at the 3' end of Sost. Naturally occurring nucleic acids in Sost encoding the last six ELENAY amino acids were added using mutagenesis.

Example 26.

In this Example, the chick Wise-FLAG sequence was inserted into the pCS2+ vector by procedures discussed in Example 19. The chick Wise sequence was placed in the pCS2+ vector using the EcoRI and SpeI/XbaI nucleases by cloning. The pCS2+ vector also contained T7, ClaI, BamHI, Sp6, and CMV sites. The chick Wise polypeptide was expressed and used to determine binding to LRP and BMPs.

Example 27.

This Example briefly describes the insertion of a mouse Sost sequence into the pcDNA3.1/V5-His-TOPO® vector. This TOPO® vector includes a CMV promoter, T7 promoter/priming site, multiple cloning site, V5 epitope, polyhistidine tag, SV40 promoter, neomycin resistance gene, and ampicillin resistance gene. Mutagenesis permitted creation of the

wild type Sost-V5 vector using the following steps: (1) addition of the sequence encoding six ELENAY amino acids, and (2) addition of the EcoR I site to the 5' end of the Sost sequence.

Example 28.

Human wild type LRP6 and mutant LRP6-Δ3,4 gene constructs in the pET28b vector were created and characterized. These gene constructs can then be utilized for the production of the corresponding mutant LRP6-Δ3,4 protein molecule. After cloning the foregoing LRP6 gene construct into the pET28b vector by the method previously described in Example 3, the pET28b vector DNA was digested with BamHI and XhoI enzymes to yield the LRP6 sequence in soluble form for further characterization. This nucleic acid sequence was not linked to the transmembrane.

The EcoRV site was then mutated within the vector backbone using the Stratagene II QuikChange XL-Site Directed mutagenesis kit. This kit's procedure is used to make point mutations, amino acid substitutions, frame shift mutations, or insertion of single or multiple adjacent amino acids in Wise and Sost genes that encode polypeptides. The pET28 vector was digested with XhoI and EcoRV. The purified BamHI/EcoRV restriction enzyme fragment was cloned into pET28b. The first band corresponded to EGF1,2; and the second band corresponded to EGF3,4. The LRP6-derived EGF1,2 fragment was cloned into the pET28b vector containing BamHI and EcoRI sites by homologous recombination as previously described in Example 13. The Stratagene mutagenesis kit was used to obtain mutations in the pET28b vector containing the LRP6-derived EGF1,2 sequence. Subsequently, XhoI, NotI and EcoRV sites were introduced into the multiple cloning site of the pET28b vector. These sites permitted opening of the circular nucleic acid sequence with EcoRV and BamH endonucleases to allow insertion of

the LRP6-derived EGF1,2 fragment into the pET28b vector. LRP6-Δ3,4 protein was then expressed from the pET28b vector.

Example 29.

This Example relates to the creation of the human LRP5Δ3,4 mutant-containing pET28b vector. Similarly, an LRP5 Δ-4 mutant-containing pET-28b vector can be made. A human LRP5 nucleic acid sequence inserted into the CS2+ vector was obtained. The coding sequence for LRP5 in this vector runs from the EcoRI site to the XbaI site. The intact LRP5 was obtained by digestion with EcoR I and Xba I nucleases. As in Example 18, the purified BamHI/XbaI fragment was then digested with the XhoI enzyme to yield two bands, corresponding to LRP5 EGF1,2 and EGF3,4 fragments. As previously, the LRP5 EGF1,2 sequence was inserted into the p28b vector containing EcoRI and XhoI sites. Site-directed mutagenesis was used to (1) remove the stop codon 5' to the actual start site and (2) delete extraneous nucleic acids located 5' to the start of the LRP sequence. The LRP Δ3-4 and LRP Δ3-4 vector subsequently can be used to independently transfect E. coli cells for production of LRP Δ3-4 and LRP Δ3-4 polypeptide molecules respectively.

Example 30.

This Example relates to the creation of the secreted LRP5-myc CS2+ vector. The human LRP5 containing pCS2 vector was obtained. Stratagen site-directed mutagenesis resulted in the following sequence modifications: (1) addition of the Myc tag upstream of the transmembrane domain, and (2) addition of XbaI and XhoI sites flanking the Myc tag region. Removal of the LRP5 sequence encoding the region that tethers the protein to the membrane was performed by digestion with XbaI nuclease. The resultant religated nucleic acid sequence encoded a secreted form of LRP5, lacking the tethered portion.

Example 31.

Hybridoma cell lines were prepared that can secrete monoclonal antibodies reactive with Wise wild type proteins, polypeptides, whole molecules, and fragments. The technology for producing monoclonal antibodies is well known. *See* generally E. A. Lerner, "How To Make A Hybridoma", Yale J. Biol. Med., 54, pp. 387-402 (1981); M. L. Gefter et al., "A Simple Method For Polythylene Glycol-Promoted Hybridization Of Mouse Myeloma Cells", Somatic Cell Genet., 3, pp. 231-36 (1977). Briefly, murine X63AG8.653 myeloma cells are fused to lymphocytes isolated from spleens of mice immunized with a preparation comprising of Wise polypeptide (*e.g.*, wild type Wise polypeptide SEQ ID NOS 45, 114-119), and the culture supernatants of the resulting hybridoma cells are screened as described herein for anti-Wise antibody binding activity. The myeloma cell line is HAT-sensitive, wherein growth in HAT medium selects for growth of HAT-resistant hybridoma cells.

To prepare Wise protein Immunogen, KLH-Immunogen is made. Wise Immunogen may be derived from Wise proteins or polypeptides. Representative Wise wild type proteins and polypeptides are SEQ ID NOs 45, 52, 104-106, and representative Wise mutant polypeptides are SEQ ID NOs 114-119. Each Balb/c mouse is immunized subcutaneously with 0.2 ml of a preparation containing about 100 μg of Wise polypeptide in PBS ("Immunogen") mixed 1:1 with Complete Freund's Adjuvant (CFA). Wise polypeptide was produced according to the method described in Examples 20-21. The Wise Immunogen polypeptide can be derived from wild type Wise molecules, as specifically described in SEQ ID NOs 45, 52, 104-106, 114-119. Shortened Wise polypeptide molecules are SEQ ID NOs 115-119. Three days after the final booster injection, mice are exsanguinated, antisera titrated, and isolated spleen cells are fused with the

non-secreting mouse myeloma cell line, SP2/0 Ag 14 (ATCC Designation CRL 8287). Thielmans, K., et al., J. Immunol. 133:495 (1984).

Prior to fusing, the resultant mouse antisera are titered to determine the concentration of anti-Wise antibodies made by each mouse. Pre-immune sera noted above are diluted in the same manner as the immune sera and used as controls. Microtiter wells are coated with 1.5 μg of BSA-Wise antigen prepared by incubating bovine serum albumin (BSA from Calbiochem, Catalog #12657, as described by Makita et al., J. Biol. Chem., 267(8), pp. 5133-5138 (1992). The antigen coated wells are sealed with Mylar sealing tape (Corning) and incubated overnight at 4°C. The microtiter plates are subsequently washed and blocked in a BSA-containing solution. After incubation, the microtiter plates are washed and 100 μl of a goat anti-mouse IgG (gamma chain specific) horseradish peroxidase-conjugated antibody (Sigma) is added to all wells and incubated. Ortho-phenylenediamine (OPD) Peroxidase Substrate (Sigma) is added to all wells and incubated. After the incubation period, the plates are read at 450 nm on a microtiter plate reader.

Anti-Wise antibodies are further characterized by their reactivity with the mouse bone, tooth, kidney, and other tissue, including but not limited to osteoblasts and osteoclasts. Monoclonal or polyclonal anti-Wise antibodies can be tested in an immunohistological assay using tissues, biochemically in an immunoprecipitation assay, and functionally in a Wnt pathway activation or inhibition assay. Briefly, anti-Wise antibodies are tested for reactivity with a panel of mouse sectioned or whole mount tissues and by immunofluorescence staining with fluorescein or rhodamine conjugated goat anti-mouse or rabbit immunoglobulin heavy or light chain reagents (TAGO, Burlingame, CA) using standard techniques. *See* Thielmans, K., et al., J. Immunol. 133:495 (1984) and Samoszuk, M.K., et al, Hybridoma 6:605 (1987). Other

colorimetric immunological reagents may be utilized in this immunohistological method. Alternatively, tissue-derived cell suspensions can be analyzed by either fluorescence microscopy or flow cytometry using a fluorescence activated cell sorter (Becton Dickinson FAXS 440, Mountain View, CA).

In a biochemical functional assay, anti-Wise antibody may be used to bind Wise protein or polypeptide, thereby inhibiting binding of Wise to LRP. Wise-FLAG and LRP-MYC reagents are made such that addition of anti-Wise antibody prevents Wise binding to LRP. In addition, anti-Wise antibody may immunoprecipitate Wise-FLAG, forming an antibody-antigen complex that is then detectable on Western blot analysis. Therefore, this assay may be used to detect anti-LRP antibody activity in functional inhibition of Wise-LRP binding. This functional assay is used as a screening tool to obtain antibodies, both monoclonal and polyclonal, which functionally bind to Wise protein *in vitro* and *in vivo* and prevent Wise binding to LRP. Similarly, anti-LRP antibodies may be screened. It is predicted that such therapeutic anti-Wise antibodies and anti-LRP antibodies can be used *in vitro* and *in vivo* to increase osteoblast number and bone mineral density and bone deposition.

In a luciferase assay, anti-Wise antibody may function to activate the Wnt pathway. Here, Human293 cells are used wherein anti-Wise antibody binds to Wise and prevents such Wnt pathway inhibition.

Upon completion of testing of anti-Wise antibodies in at least one of the above assays, those mouse sera and rhybridoma clones producing monoclonal antibodies that are reactive against Wise present in bone cells (osteoblasts, osteoclasts) can be selected for further expansion and processing. Goat antisera containing polyclonal antibodies reactive against Wise can also be produced.

Hybridoma production can be carried out by fusing the mouse spleen cells with the myeloma X63AG8.653 cell line by the procedure described in Harlow, E. and D. Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. The Sp-2/0 myeloma cell line may also be used. Briefly, spleen cells are mixed with HAT-sensitive X63AG8.653 myeloma cells and fused with polyethylene glycol (PEG) (*e.g.*, 50% PEG 4000, Sigma Chemicals). Subsequent to fusion of spleen cells with the myeloma cell line, 1 drop of the 50 ml fusion mixture is added to each of 96 wells in 10 microwell cell culture plates (Corning). After culture of clones in selection media, hybridoma cultures are screened for antibody production to Wise antigen as follows:

Wise-polypeptide coated wells are prepared. Further, BSA is coated on wells following the same coating procedure as with BSA-Wise to detect any nonspecific binding. The antigen coated plates are used to screen cell culture supernates from each of the parental cultures. The parental supernates are added to one well of BSA-Wise-coated microtiter plate and to one well of BSA coated plate. The plates are incubated and washed. Goat anti-mouse IgG (gamma chanin specific) horseradish peroxidase-conjugated antibody is added to each well. Parental cultures are identified that produce absorbance readings exceeding 0.3 O.D. on the BSA-Wise wells and no reactivity on the BSA coated wells. The latter parental cultures are expanded in culture in 24 well macrowell plates (Corning) and upon further supernatant/antibody evaluation, three parental cultures are re-cloned (secondary cloning). Following a procedure described in Harlow and Lane, supra, the parental cultures are diluted in RPMI 1640 culture medium containing 20% fetal bovine serum to give a cell density of 0.5-10 cells per well on wells that are precultured with splenocyte feeder cells.

After two weeks parental cell culture supernates are tested to determine the wells that are positive for monoclonal anti-Wise antibody activity using the screening procedure above. Positive wells are cloned and subcloned. Clonal cultures can be identified with high viability and producing the highest titer antibody to BSA-Wise in the aforementioned antibody screening assay. Secondary and tertiary subcloning of the latter is done to assure monoclonality and stability of the resultant clones. Comparative affinity analysis may be performed in accordance with Macdonald et al. (Macdonald, R. A. et al. 1988. Journal of Immunological Methods, 106:191-194). The cells from each culture are prepared in accordance with Harlow and Lane, supra, for frozen storage in ampoules in liquid nitrogen. Each single clone is expanded in culture and adapted to a protein-free medium (MaxiCell/Hybridoma-PF Medium, Cat. No. N10105, Atlanta Biologicals, Norcross, Ga.) for monoclonal antibody production. Thus, anti-Wise monoclonal antibodies are prepared that can be utilized in subsequently described bone deposition experiments.

Next, monoclonal antibodies from subclones can be tested against Wise wild type and mutant polypeptides for binding by direct ELISA and competition ELISA methods. For direct ELISA, BSA-Wise is coated on microtiter plates, the unbound sites are blocked by incubation with Assay Buffer (25 mM borate, pH 8.0, 150 mM NaCl, 0.01% EDTA and 1% BSA). The plate is washed 6X and increasing concentrations of monoclonal antibody (mAb) in Assay Buffer are added. After this incubation, the plate is again washed and incubated with alkaline-phosphates labeled goat anti-mouse antibodies (Cappel, Durham, N.C.) diluted 1:1000 in Assay Buffer. The unbound antibodies are removed by extensive washing and the bound antibodies are detected by addition of p-nitrophenylphosphate (PNPP). The optical density at 410 nm is recorded.

The competition ELISA can be performed by pre-coating microtiter plates with BSA-Wise wild type and mutant polypeptides and blocking with Assay Buffer. The plate is washed, and monoclonal anti-Wise antibody is added with increasing concentrations of the Wise wild type and mutant polypeptide antigen competitors, simultaneously incubating the mixture for 1 hr at 37° C. The unbound materials are removed by extensive washing and the bound mAb is detected with alkaline phosphatase labeled anti-mouse antibodies similar to the direct ELISA method above. All washes are in TBS-T wash solution; all incubations proceeded for 1 hr at 37° C. It is predicted that monoclonal antibodies directed against Wise immunogen will bind specifically to Wise wild type molecules. Such anti-Wise monoclonal antibodies, depending on their reactivity profiles, may or may not bind to Wise mutant molecules that do not bind to LRP.

Fab fragments of anti-Wise antibodies can be prepared. After purification of anti-Wise IgG antibody, Fab fragments are prepared by papain cleavage. Mercuripapain is pre-activated with 10mM cysteine in 1.25 MM EDTA for 15 min at 37° C, then added to the IgG antibody (5-10 mg/ml) at a 1:50 to 1:200 (w/w) ration of enzyme to antibody. The period of incubation at 37° C ranged between 15 min to 5 hours to determine the optimum time of incubation for maximal Fab yield. Addition of iodacetamide (20 – 50 mM) stopped the cleavage process. Conditions are optimized by SDS-PAGE. analysis of resultant reaction products.

Thus, anti-Wise monoclonal antibodies and Fab "mini-antibody" fragments are prepared that can be utilized in subsequently described experiments below wherein such antibodies are delivered in liposomes to bone cells (*e.g.*, osteoblasts) for the purpose of increasing bone deposition and bone mineral density *in vitro* and *in vivo*. Anti-Wise Fab fragments are predicted to have greater anti-Wise inhibitory activity than whole anti-Wise antibody. Both anti-Wise

antibodies and their corresponding Fab fragments are expected to bind to Wise molecules in osteoblasts and prevent Wise molecule binding to LRP molecules (*e.g.*, LRP5, 6).

Example 32.

Hybridoma cell lines can be prepared that can secrete monoclonal antibodies reactive with Sost wild type proteins, polypeptides, whole molecules, and fragments according to the procedure described in Example 31 above. Briefly, murine myeloma cells are fused with murine splenic lymphocytes from mice immunized with Sost-derived antigen. Hybridomas making monoclonal antibodies reactive against Sost antigen are selected, grown, and monoclonal antibodies can then be screened with Sost antigen in EIA assays, histological tissue staining assays, immunoprecipitation assays, and functional assays as previously described. Fab fragments of anti-Sost antibodies can be prepared by standard papain and pepsin enzymatic digestion methods.

Example 33.

This Example relates to detection and analysis of the wild type, and also genetically modified, Wise cysteine knot regions in mammalian cells. Similarly, detection and analysis of the Sost cysteine knot region from wild type or genetically modified cells may be executed. In this procedure, murine C57BL/6 osteoblasts, producing Wise polypeptide are isolated. Other isolated or cultured mammalian cells can be used. Genetically modified Wise molecules can be made as presented in Example 18-21, wherein the stop codon in the Wise Neo-lacZ cassette, which is subsequently inserted into ES cells, encodes a truncated Exon 2 polypeptide product that comprises part of the cysteine knot region of Wise. After PCR amplification of these shortened Wise nucleic acid sequences by standard molecular biology cloning techniques, such

sequences are placed on Southern blots for gDNA and on Northern blots for mRNA species. J. Sambrook and D.W. Russell, Molecular Cloning: A Laboratory Manual, 3rd edition (2001).

More specifically, Wise gene nucleic acid fragment sequences for SEQ ID NOs 1 – 5 and 126 - 128 may be made and amplified by standard PCR technologies. These Wise nucleic acid sequences encode corresponding polypeptides. A smaller Wise gene DNA or RNA probe sequence corresponding to SEQ ID NO 1 can be synthesized (see SEQ ID Nos 136-140). Alternatively, site specific mutagenesis or *in vitro* transcription methods may be utilized. The DNA probe can then be labeled with P-32 cytosine (CTP). Alternatively, C-14, H-3, or other radiolabels or nonradioactive labels (*e.g.*, DIG) may be used. In addition, the RNA probe can be labeled with P-32 uracil. Once Wise DNA probes are labeled with P-32 cytosine, these radiolabeled probes may be hybridized to nucleic acids extracted from Wise-containing cells to characterize such Wise genes after Southern blot analysis. Similarly, radiolabeled Wise RNA probes may be hybridized to nucleic acids from Wise-containing cell extracts. It was observed that these Wise RNA fragments detected the presence of Wise nucleic acid sequences in the cell extracts.

Example 34.

Wise antigens to be prepared for immunization and to be used as standards in immunoassays include, but are not limited to, Wise wild type polypeptide whole molecule and polypeptide fragments. In addition, the corresponding Wise-derived nucleic acid molecules to the aforementioned polypeptide molecules were produced as antigens for immunizations and standards. Both Wise-derived polypeptide and nucleic acid antigens are prepared as previously described herein.

Goat and rabbit polyclonal antibodies and mouse monoclonal antibodies to the Wise-derived wild type and mutant polypeptide and nucleic acid molecules are prepared by methods that are known to those of skill in the art. E. Harlow and D. Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988. Similarly, goat and rabbit polyclonal antibodies and mouse monoclonal antibodies may be made to Sost-derived wild type and mutant polypeptides and nucleic acid molecules. The procedure for production of monoclonal antibodies to specific antigens has been described in detail herein. Once monoclonal and polyclonal antibodies to Wise-derived polypeptide and nucleic acid molecules have been made, they can be utilized in immunodiagnostics kit assays for the detection and quantitation of the Wise-derived molecules.

Example 35.

A Sost-specific monoclonal antibody can be made by the procedure as delineated in Examples 32 and 33. Sost-specific monoclonal antibodies may be made against Sost wild type and mutant proteins and polypeptides. These antibodies would inhibit the binding of Sost to LRPs.

Example 36.

This Example relates to the production of monoclonal antibody to the terminus region of LRP5 which binds to Wise protein. This LRP5 terminus region also binds to Sost protein. The anti-LRP5 antibody is predicted to inhibit binding of Wise to LRP5 and thereby result in phenotypic changes such as increased osteoblast number, increased bone mineral density and bone deposition, and tooth and ocular phenotypic changes. Similarly, the anti-LRP5 antibody is predicted to inhibit binding of Sost to LRP5, resulting in similar phenotypic changes.

LRP 5 Δ3-4 mutants are made as described in Examples 28 and 29. Such LRP5 Δ3-4 mutant nucleic acid sequences can be inserted into either p28b vectors as described in Examples 28 and 29, or Neo-lacZ cassettes (without stop codons) as described in Example 13. E. coli cells containing the p28b vector with the LRP5 mutation, and ES cells containing the Neo-lacZ cassette with the same mutation are cultured, lysed, and LRP5 Δ3-4 purified.

Monoclonal antibody can be made to LRP5 by immunization of mice with LRP5 as described in Example 32, hybridization of LRP5 immunized mouse splenic lymphocytes with HAT-sensitive myeloma cells, and selection of HAT-resistant hybridoma cells secreting antibodies that bind LRP5. Once clones are identified that secrete antibody binding to LRP5, clones are futher screened for failure to bind LRP5 Δ3-4 in EIA and functional assays as described in Example 32. Such hybridoma clones that bind to wild type LRP5 molecules yet do not bind to LRP5 Δ3-4 molecules are deemed to be putative anti-LRP5 Δ3–4 region-epitope specific antibodies (LRP5 Δ3-4). Photoreactive chemical conjugation of H3-radiolabeled antibody combining sites to the LRP5 molecule can verify this antibody-specific attachment to the terminal amino acid sequence of LRP5.

Example 37.

This Example relates to the production of monoclonal antibody to the terminus region of LRP6 which binds to Wise protein. The anti-LRP6 antibody is predicted to inhibit binding of Wise to LRP6 and thereby result in phenotypic changes such as increased osteoblast number, increased bone mineral density and bone deposition, and tooth and ocular phenotypic changes. Similarly, the anti-LRP6 antibody is predicted to inhibit binding of Sost to LRP6, resulting in similar phenotypic changes.

LRP 6 Δ3-4 mutants are made as described in Examples 28-29. Such LRP 6 Δ3-4 mutant nucleic acid sequences can be inserted into either p28b vectors as described in Examples 28-29, or Neo-lacZ cassettes (without stop codons) as described in Examples 13. E. coli cells containing the p28b vector with the LRP6 mutation, and ES cells containing the Neo-lacZ cassette with the same mutation are cultured, lysed, and LRP6 Δ3-4 purified.

Monoclonal antibody can be made to LRP6 by immunization of mice with LRP6 as described in Example 32, hybridization of LRP6 immunized mouse splenic lymphocytes with HAT-sensitive myeloma cells, and selection of HAT-resistant hybridoma cells secreting antibodies that bind LRP6. Once clones are identified that secrete antibody binding to LRP6, clones are further screened for failure to bind LRP 6 Δ3-4 in EIA and functional assays as described in Example 32. Such hybridoma clones that bind to wild type LRP6 molecules yet do not bind to LRP 6 Δ3-4 molecules are deemed to be putative anti-LRP6 Δ3-4 region-epitope specific antibodies (LRP6 Δ3-4). Photoreactive chemical conjugation of H3-radiolabeled antibody combining sites to the LRP6 molecule can verify this antibody-specific attachment to the terminal amino acid sequence of LRP6.

Example 38.

This Example relates to the production of biotinylated liposomes which are then linked to monoclonal antibodies specific for osteoblasts through an avidin linkage. These anti-osteoblast antibody-armed liposomes can be utilized to deliver encapsulated anti-Wise antibody to osteoblasts. Similarly, encapsulated anti-Sost antibody may be made and delivered to osteoblasts. Liposomes may be armed with anti-osteoblast (anti-OB) antibodies that react with either mouse or human osteoblasts as described herein. Delivery of anti-Wise antibodies to

osteoblasts using encapsulated liposomes is anticipated to result in increased osteoblast growth and proliferation with concommitant increased bone deposition.

Biotinylated phospholipids are initially prepared. Biotinylated phospholipids are prepared by dissolving phosphatidylethanolamine (PE, 5.1 mg) or phosphatidylserine (PS, 3.9 mg) in a solution (170 µl for PE; 130 µl for PS) of chloroform-methanol (2:1) with biotinyl N-hydroxysuccinimide ester (BNHS, 3.3. mg) (Sigma Chemicals, St. Louis, MO). 10 µl is added of a chloroform solution containing 15% (v/v) triethylamine. After a two hour incubation of the reaction mixture at ambient room temperature (18° C), the crude mixture is stored at -70° C.

The crude biotinylatedlipid is then purified by high-performance liquid chromatography (HPLC) using a Waters system (Waters Associates, Milford, MA) with two solvent delivery units (M-45 and Model 510) and a Model 680 gradient controller. Separations are performed using a stainless steel column (250 x 4.6 mm i.d.) packed with 5 µm Lichrosorb Si-100 silica (Merck, Darmstadt, Germany) at room temperature with a flow rate of 1 ml/min. After a first wash with solvent A (n-hexane/2-propanol/sater in a ratio of 60:80:14, v/v/v), Solvent B (n-hexane/2-propanol/water 60:80:7, v/v/v) is added until a new baseline is stabilized.

10 µl of the crude biotinylated lipid starting reaction mixture containing 390 nmol lipid is applied to the HPLC column using a Hamilton syringe, and the elution is monitored utilizing an M-441 UV detector (214 nm). The column is eluted for 5 min with solvent A, then with a 20 min linear gradient between 0 and 100% solvent B in A. Solvent B is then passed over the column until a stable baseline is obtained.

The average retention times of BPE and BPS are 20.7 min (17-22) and 27.1 min (26-28), respectively. The HPLC peaks are collected in a Gilson Microfractionator, and the eluted

material is pooled. The solvent is then evaporated under a stream of nitrogen, and the biotinylated lipid is stored at -70° C.

Both the initial crude reaction mixture and the HPLC-purified BPE and BPS fractions are analyzed by thin-layer chromatography (TLC) in silica gel-coated plates (Riedel-de Haen, Germany). For BPE plates, a chloroform/methanol/water (80:25:2) solution is used; and for BPS plates, a chloroform/methanol/acetic acid (30:4:3) solution is used. Phospholipid visualization occurs through one of three methods: (1) exposure to iodine vapors, (2) a biotin-specific spray (dimethylaminocinnamaldehyde) *See* D.B. McCormick and J.A. Roth Methods in Enzymology 148A: 383 (1987), or (3) a phosphate-specific spray. *See* V.E. Vaskovsky and E.Y. Kostetsky, J. Lipid Res. 9: 396 (1968). All three staining methods reveal that BPE has an $R_f = 0.65$, and BPS has an $R_f = 0.55$.

Biotinylated liposomes are then prepared. Biotinylated phospholipids (BPE or BPS) are dissolved in chloroform/methanol (2:1) and molar equivalents of each corresponding lipid (BPE or BPS) are added to 12 mm x 75 mm glass tubes to yield the final percentage of biotinylated lipid desired (*e.g.*, 5, 10, 20%). Concentrations of 0.01 to 1 mol% of total lipid are achieved.

To prepare liposomes, the biotinylated lipid/native lipid mixture (*e.g.*, 2 μmol of the stock lipid mixture in chloroform/methanol) is evaporated to dryness under a stream of nitrogen and then placed in a vacuum dessicator overnight. The lipid is resuspended by syringe injection (*e.g.*, 50 μl lipid in chloroform/methanol into 1.0 ml PBS) in a final concentration of 1 mg/ml in PBS, pH 7.2-7.4, then sonicated under nitrogen in an ice-cooled chamber for 10 min in a Branson Sonifier Model 130. The resulting suspension is centrifuged at 10,000 rpm for 20 min, and the biotinylated liposomes in the supernatant fraction used within 24 hours after preparation.

To encapsulate anti-Wise antibodies, the biotinylated lipid/native mixture is resuspended by injection (*e.g.*, 50 µl lipid in chloroform/methanol into 1.0 ml PBS) into an anti-Wise antibody-containing PBS solution. After sonication and centrifugation at 10,000 rpm for 20 minutes, anti-Wise antibody-biotinylated liposomes are purified by one of the following procedures: (1) in one preferred procedure, liposome preparations are centrifuged at 13,000 x g in a microcentrifuge; pelleted liposomes are washed with PBS, and pelleted liposome fractions are resuspended in PBS buffer for use; (2) in another method, liposome preparations are passed over a Sephadex 200 column (Pharmacia, Piscataway, NJ) in PBS. The liposomes are eluted in the PBS void volume, with free protein and contaminants appearing in subsequent collection.

Once the liposomes are prepared, Fab fragments of anti-osteoblast cell (anti-OB) antibodies must be prepared. Rat anti-mouse Thy-1 monoclonal antibody and mouse anti-human Thy-1 monoclonal antibody are obtained from Pharmingen (San Diego, CA). Thy 1 is known to be an expressed surface antigen on osteoblast cells. X-D Chen, et al., Thy-1 Antigen Expression by Cells in the Osteoblast Lineage, J. Bone & Mineral Research 14(3): 362-375 (1999). Other suitable osteoblast-reactive antibodies have been described. *See, e.g.*, Aubin, J.E. et al. Monoclonal antibodies as Tools for Studying the Osteoblast Lineage, Microsc Res Tech 33:128-140; Bruder SP et al. (1996) Monoclonal Antibodies Selective for Human Osteogenic Cell Surface Antigens, Bone 21:225-235. After purification of anti-OB IgG antibody, Fab fragments are prepared by papain cleavage. Mercuripapain is pre-activated with 10mM cysteine in 1.25 mM EDTA for 15 minutes at 37° C, then added to the IgG antibody (5-10 mg/ml) at a 1:50 to 1:200 w/w) ratio of enzyme to antibody. The period of incubation at 37° C. ranged between 15 minutes to 5 hours to determine the optimum time of incubation for maximal Fab yield.

Addition of iodoacetamide (20-50 mM) stopped the cleavage process. Conditions are optimized by SDS-PAGE analysis of resultant reaction products.

Biotinylated Fab fragments of anti-OB antibodies are obtained by using an N-hydroxysuccinimidobiotin (NHS-Biotin, Sigma Chemical, St. Louis, MO). In this method, 2 mg of Fab fragments are dissolved in 1 ml of sodium phosphate buffer (PBS), pH 7.5-8.5, in a 16 x 125 mm test tube. Immediately before use, 1 mg of NHS-Biotin is dissolved in 1 ml dimethylformamide (DMF). 75 µl of the dissolved NHS-Biotin is added to the Fab containing test tube. The tube is incubated on ice (4° C) for 2 hours. The unreacted biotin may be removed by dialysis (*e.g.*, Slide-A-Lyzer Dialysis Cassette) or with a D-Salting Column (Pierce Chemical, Rockford, IL). Alternative, unreacted biotin may be removed by centrifugation of the product at 1000 x g for 15-30 minutes using a microconcentrator. After centrifugation, the sample is diluted in 0.1 M sodium phosphate, pH 7.0. The process can then be repeated twice more. The biotinylated protein may be stored at 4° C in 0.05% sodium azide prior to use.

Finally, Fab-anti-Wise liposomes utilizing biotinylated Fab molecules, biotinylated liposomes and avidin are prepared. The biotinylated Fab fragments in PBS are mixed with a twenty-fold molar excess of egg white avidin (Vector labs, Burlingame, CA; Sigma Chemical, St. Louis, MO), incubated overnight at 4° C. The excess avidin is removed by passage of the mixture over anti-human light chain affinity columns (*e.g.*, Pharmacia Sepharose 4B). Fab-biotin-avidin molecules are eluted with citrate buffer, pH-4.0, then pooled fractions are dialyzed against PBS, pH=7.0. A suspension of biotinylated anti-Wise antibody-containing liposomes is mixed with Fab-biotin-avidin solutions in PBS to yield avidin to free biotin ratios on the liposome surfaces of approximately 2:1, 5:1, 10:1, and 20:1 molar ratios. After incubation overnight at 4° C on a rotational shaker, liposomes are passed through a Pharmacia Sephadex G-

200 column. The Fab-anti-Wise liposomes are collected in the void volume and resuspended in PBS.

Alternatively, biotinylated anti-Wise antibody-containing liposomes are mixed with a twenty-fold molar excess of strepafidin, incubated overnight at 4° C, then biotinylated-avidin liposomes are passed over the anti-human light chain affinity column. Biotinylated-avidin anti-Wise liposomes are eluted with a citrate buffer, pH = 4.0, then pooled fractions are dialyzed against PBS, pH=7.0. After dialysis, biotinylated-avidin liposomes are mixed with biotinylated Fab fragments in PBS in the above approximate molar ratios. Similarly, after incubation overnight at 4° C on a rotational shaker, liposomes are passed through a Pharmacia Sephadex G-200 column. The Fab-Anti-Wise antibody liposomes are collected in the void volume and resuspended in PBS.

Example 39.

The present Example relates to *in vitro* treatment of mouse bone cells (*e.g.*, osteoblasts and osteoclasts) by anti-Wise-specific Fab liposomes armed with anti-osteoblast antibody as prepared in Example 40. The anti-Wise antibody may have specificity for Wise whole molecule or polypeptides. Similarly, anti-Sost antibody may be encapsulated in liposomes to obtain osteoblast phenotypic effects *in vitro*. First, murine bone cells are purified by fluorescence activated cell sorting (FACS) using anti-bone marker antibodies. In addition, mouse bone cell osteoblasts can be prepared essentially as described by Takahashi et al., 1988 Endocrinology 123:2600-2602; and by Tanaka et al., 1992 J. Bone Min Res. 7:S307, which are incorporated by reference herein. These bone cells are liquid nitrogen-cryopreserved in ampoules.

Bone cells are separated by fluorescence activated cell sorting (FACS) utilizing the FACStar-PLUS flow cytometer (Becton Dickinson) equipped with two 5-watt argon ion lasers

and a tunable dye laser interfaced with a Digital Equipment Corporation Vas Station-4000/90 computer and data collection/analysis software. Bone cells are prepared by suspension in MACS (magnetic sorting) buffer with fluorescein-conjugated antibody directed against mouse osteoblasts (DAKO, Carpenteria, CA) in a tube and vortexed. After incubation for 30 minutes at 4° C, cells are washed 3 – 5 times in MACS buffer, then centrifuged at 400 x g for 5 minutes at 4° C. Cells are placed in MACS buffer at 4° C for separation in the FACStar flow cytometer. Mouse bone cells are separated on the basis of the fluorescence and size. Aliquots of purified murine osteoblasts and osteoclasts cells are tested for reactivity with anti-Wise antibodies in a fluorescence sandwich immunoassay with murine monoclonal anti-Wise antibody made according to the method of Example 32 and fluorescein-conjugated goat anti-mouse IgG antibody (H & L) (DAKO, Carpenteria, CA). Cells are stained for viability (>90%) by Trypan blue staining.

Subsequent to viable bone cell isolation above, bone cells (primarily osteoblasts or osteoclasts) are incubated *in vitro* with anti-Wise antibody-containing liposomes. An aliquot of anti-Wise-liposome-bone cells are then lysed. Polypeptide molecules of the elysate are separated and characterized by SDS gel electrophoresis and Western blot analysis. Reduction of Wise binding to LRP in the presence of anti-Wise antibody in bone cells can be measured.

It is predicted that anti-Wise antibody and anti-Wise Fab fragment molecules will both inhibit binding of wild type Wise to LRP5 in osteoblasts *in vitro*. In contrast, anti-Wise antibodies and fragments should not bind to osteoclasts, nor assert an effect on osteoclast activity (*e.g.*, bone resorption). Correspondingly, based in part upon results described in Example 16 herein, it is expected that anti-Wise inhibition of Wise binding to LRP5 will result in increased growth and number of osteoblasts. Such increase in osteoblast number has previously

been associated with concomitant increases in bone deposition and bone mineral density *in vivo*, as described in Example 16. Thus, treatment with anti-Wise liposomes is predicted to result in increased bone deposition and bone mineral density in *in vivo* mouse studies.

Example 40.

The present Example relates to *in vivo* treatment of nude mice implanted with murine bone cells (*e.g.*, osteoblasts, osteoclasts) with anti-Wise antibody-containing liposomes. Congenitally athymic nude mice containing murine bone fragment implants can be used as a test system for assessing the anti-Wise antibody-containing liposomes on murine bone cell growth *in vivo* according to the procedure described herein.

Congenitally athymic homozygous CD-1 female nude scid/scid mice (SCID, Charles River Laboratories, Wilmington, MA) are housed in sterile cages, treated with antibiotics and give autoclaved food and water. At approximately 6 – 8 weeks old, SCID mice can be injected subcutaneously with cut fragments of femurs and tibias of allotypically different murine fetuses or immature pups. Balb/c mice can be used as bone donors. Intraperitoneal injection of mice with bone fragment marrow implants is an alternative rout of administration. These mice may now be referred to as "SCID-bone mice." Murine implanted bone fragment marrow grafts are allowed to "take" for approximately 6 – 8 weeks prior to injection with anti-Wise antibodies. Fetal donor bone cell suspensions are analyzed for murine allotypic markers.

As previously described herein, Fab anti-Wise antibody-containing liposomes can be prepared. $0.5 - 5.0 \times 10^6$ bone osteoblast cells are suspended in 20 ml of complete RPMI-1640 medium and injected with a Hamilton microliter syringe into each of the 6 – 8 week old murine bone marrow grafts of the SCID-bone mice. In the first experiment, Fab anti-Wise antibody liposomes (200:1; 100:1, 50:1 liposome:cell ratios) can be mixed together with bone cells prior

to injection *in vivo*. In the second experiment, bone cells can be injected into the bone fragment marrow grafts, then anti-Wise antibody-containing anti-osteoblast antibody-armed liposomes (200:1; 100:1; 50:1 liposome:cell ratios) can be injected by several routes: (1) directly into the murine bone marrow, 4, 6, and 24 hr after murine bone fragment implantation; and (2) intravenously in the mouse tail vein at 0, 4, 6, and 25 hr after murine fragment implantation. Alternatively, and perhaps preferably, anti-Wise antibody-liposomes may be mixed with osteoblasts or osteoclasts prior to placement in operably contact with the implanted bone fragment. Controls would include anti-Wise antibody-containing liposomes wherein the attached arming antibody lacks osteoblast-binding specificity, and liposomes lacking anti-Wise antibody.

The effect of anti-Wise antibody-liposome treatment on bone cells can then be assessed by the following procedure. Growth of bone cells (*i.e.*, osteoblasts, osteoclasts) can be analyzed by examining cells harvested from SCID-bone mouse bone fragment marrow implants at 1, 2, 4, 8, 16, and 32 weeks after anti-Wise antibody-liposome injection. Harvested cells can be analyzed by flow cytometry in the FACScan system after suspension in complete RPMI-1640 medium, washing in RPMI, lysing of red blood cells with ammonium chloride, and staining with immunofluorescent reagents. Immunofluorescence sandwich markers including fluorescein- or rhodamine-conjugated goat anti-mouse IgG (H & L) antibody can be used in conjunction with murine monoclonal anti-Wise anti-body. Histological sections of bone, bone marrow, spleen, lymph node, lung and other tissue can also be prepared 1, 2, 3, and 4 months after bone cell implantation, sectioned, and stained with immunofluorescence reagents described above or with hematoxylin and cosin-stained formalin-fixed and paraffin-embedded specimens compared with specimens from untreated, control SCID-bone mice in which no osteoblast or osteoclast cells are

injected. Significantly, SCID-bone mice may be analyzed for treatment with anti-Wise antibody-liposomes to determine efficacy of such liposomes to increase in growth and number of osteoblasts which is expected to result in increased bone deposition in this *in vivo* SCID nude mouse model system. Moreover, SCID-bone mice may be used to assess anti-human Wise antibody treatment effects utilizing xenogeneic human bone fragment transfers into such SCID-bone mice as described herein.

Example 41.

This Example relates to injection of anti-Wise antibodies into the pups of the C57BL/6 mouse strain to determine their positive effects on Wise-regulated phenotypes. Alternatively, the 129 mouse strain may be used. Monoclonal and polyclonal anti-Wise antibodies specific for wild type Wise polypeptide molecules were made as described in Example 31 above. The antibody can be directed to the cysteine knot-containing region of Wise. Similarly, anti-Sost antibodies may be injected into mouse pups to determine phenotypic and therapeutic changes.

In this procedure, C57BL/6 mouse pups are injected with therapeutic doses of anti-Wise antibody in a pharmaceutical carrier such as sterile endotoxin-free phosphate buffered saline (PBS) at 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 days post partum. Alternatively, anti-Wise antibody Fab fragments may be used in a suitable pharmaceutical carrier medium. Bone mineral density of injected mice is compared to that of uninjected control mice as described in Example 16. It is anticipated that anti-Wise antibody treatment will result in increased bone mineral density and increased bone deposition in injected mice as compared to controls.

It is also predicted that anti-Wise antibody treatment will result in phenotypic changes in eyes and teeth as described in Wise mutant mice in Examples 15 and 17 above. Thus, anti-Wise antibody injected mice are expected to exhibit loss of optic nerve fibers and increased rod and

cone layers in the retina as shown in Example 15 in Wise mutant mice. Anti-Wise antibody injected mice are predicted to manifest molar and incisor tooth abnormalities similar to those of Wise mutant mice as demonstrated in Example 17. An additional incisor tooth phenotype not present in the wild type mouse may be observed. In addition, anti-Wise antibody injected mice may show an additional Ml molar tooth, with an additional associated root. Anti-Wise antibody injected mice may also exhibit reverse orientation patterning of molar teeth, with possible fusion of Ml and M2 teeth.

Example 42.

In this Example, kit components for detection and quantitation of Wise wild type and mutant polypeptides and fragments are described. Immunodiagnostics methodologies utilized in these kits are modifications of general and specific principles well known in the art. E. Harlow and D. Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988, and E.T. Maggio, Ed., Enzyme-Immunoassay, CRC Press, Florida, 1980 are incorporated by reference herein.

Sandwich enzyme immunoassay kit components are as follows: 96-well microtiter plates coated with anti-Wise antibody, diluent buffer, Wise standards, horseradish peroxidase (HRP)-conjugated mouse anti-Wise antibody, ortho-phenylenediamine (OPD) substrate solution, containing H_2O_2, and 2N sulfuric acid stop solution.

Competitive enzyme immunoassay kit components are as follows: 96-well microtiter plates coated with wild type or variant Wise molecules, diluent buffer, Wise wild type and variant standards, horseradish peroxidase (HRP)-conjugated mouse anti-Wise antibody, ortho-phenylenediamine (OPD) substrate solution, containing H_2O_2, and 2N sulfuric acid stop solution. Similarly, Sost immunoassay kits may be prepared by substituting anti-Sost antibody for anti-

Wise antibody, and Sost standards for Wise standards as components in the above described Wise kit.

Example 43.

In this Example, an immunoprecipitation protocol and subsequent Western Blot protocol are described for analysis and characterization of various Wise-derived proteins and polypeptide molecules. Similarly, immunoprecipitation and Western blot analysis and characterization may be executed for Sost-derived proteins and polypeptide molecules. Western blot kits based on the methodology described herein may also be produced.

Western blot kits will contain the following components: Wise-derived protein and polypeptide molecule standards, primary goat antibody against Wise, secondary alkaline phosphatase-conjugated anti-goat antibody, blocking buffer, diluent buffer, and substrate development solution.

The immunoprecipitation protocol involves a technique for separation of Wise-derived polypeptide molecules from whole cell lysates or cell culture supernatants. Wise-derived polypeptide molecules may be wild type or mutant molecules; and these molecules may be obtained from mammalian cell cultures (*e.g.*, osteoblasts) or from bacterial cells (*e.g.*, E. coli) or mammalian cells. After immunoprecipitation binding to anti-Wise antibody and separation of these Wise-derived polypeptide molecules, the Wise molecules can be identified, biochemically characterized, and expression levels quantitated. Sost-derived polypeptide molecules may be similarly immunoprecipitated.

In initial immunoprecipitation runs, approximately 5-10 μg of anti-Wise-derived polypeptide molecule antibody is added to an Eppendorf tube containing the cold precleared lysate containing Wise polypeptides. Alternatively, antibodies recognizing the MYC tag may be

utilized for these immunoprecipitations of Wise polypeptides. Reduced and nonreduced Wise-derived polypeptide molecules are prepared to run alongside prestained molecular weight standards for use on SDS-PAGE gels.

In the R&D System Immunostaining procedure, Western Blot membranes are blocked in Blocking Buffer, incubated with primary goat anti-Wise polypeptide antibody, incubated with secondary antibody (*e.g.*, alkaline phosphatase conjugated anti-goat IgG antibody), incubated with Substrate Development solution, dried, and blocked in Blocking Buffer. Block unoccupied protein binding sites on membrane by placing membrane in Blocking Buffer on a rocker/shaker. Primary antibody (*e.g.*, goat anti-Wise polypeptide molecule antibody) in Diluent Buffer is added to the membrane and incubated. After washing, incubate blots with 20 mL of secondary antibody (*e.g.*, TAGO alkaline phosphatase-conjugated rabbit anti-goat IgG antibody) in Diluent Buffer and incubated. Wash membranes, incubate and then add Substrate Development Solution to membrane. Stop substrate development after incubation by pouring off Development Solution and rinsing membrane in deionized water.

In summary, this Western blot methodology can be used to identify, biochemically and immunologically characterize, and quantitate Wise and Sost polypeptide molecules derived from wild type and/or mutants in both mammalian and bacterial cell culture systems. In addition, Western blot kits may be produced utilizing Wise-derived and Sost-derived molecule standards, antibodies, and kit components described and utilized in the above-described methodology.

Example 44.

In this Example, hybridization kits are described for the detection of Wise wild type and Wise variant nucleic acid sequences. Wise wild type and variant nucleic acid sequence molecules are prepared by either PCR methodology [Mullis, U.S. Pat. No. 4,683,195; Mullis,

4,683,202], including real time PCR techniques, or conventional cloning technology as described in Examples 19-20. Probe nucleic acid sequences can be produced in vectors as described previously. As alternatives to PCR methodology, isothermal techniques [Guatelli et al., Proceeding of the National Academy of Science 87: 1874-1878 (1990)], transcription based methods [Kwoh et al., Proceedings National Academy of Science 86: 1173-1177 (1989)], and QB replicase techniques [Munishkin et al., Nature 33: 473 (1988)] may be used. DNA or RNA primers are prepared containing desired Wise or Sost probe sequences. For example, a nucleic acid probe can be prepared to different portions of Wise nucleic acid sequences. Similarly, probes can be prepared for nucleic acid sequences that encode inactive Wise polypeptide variants that either do not bind to LRP5 or LRP6 or, alternatively, that, when inserted into mammalian cells, cause phenotypic increases in bone deposition or bone mineral density. [Kemp et al., Proceedings of the National Academy of Science 86: 2423-2427 (1989)].

Wise wild type molecule and Wise variant cDNA synthesis and DIG labeling is as follows: Heat 10-15 μgWise sample RNA with 1.7 μl random primers (3 ug/ul; Invitrogen Cat. No. 48190-011) and 15.9 μl H_2O at 70° C. Snap cool on ice and centrifuge. To each reaction tube, add DIG-dCTP. Add Master mix as follows: First Strand Buffer, DTT, dNTPs (25 mM each dA/G/TTP, 10 mM dCTP), SuperScript II (200 U/ul; Invitrogen Cat. No. 18064-014). Incubate reaction at 25° C, followed by 42° C incubation.

While incubating the above reaction mixture, slides are prepared for hybridization as follows: Incubate the prehybridization solution in a Coplin jar at 63° C to equilibrate. Place slides in the pre-heated solution and incubate at 63° C. Prepare two staining troughs, one with MilliQ H_2O and the other with isopropanol. Place slides in slide rack and immerse in first trough to rinse in MilliQ H_2O with vigorous shaking. Transfer the rack into the second trough and rinse

in isopropanol. Dry slides by centrifugation on a microtiter plate rotor on absorbent cloth. Store slides in slide box prior to hybridization.

Briefly centrifuge the labeling reaction tubes. Add 10 µl 1N NaOH and heat at 70° C to hydrolyze the RNA. Neutralize by adding 1 N HC1. Using the MinElute PCR purification kit (Qiagen Cat. No. 28004), combine DIG-labeled cDNA samples in a single Eppendorf tube and add Buffer PB. Apply to MinElute column in collection tube and centrifuge. Purple coloration of the membrane indicates efficient labeling of both cDNA samples. Add 50 µl Buffer PE to MinElute column and centrifuge to dry the membrane. Add 10 µl MilliQ H_2O pH 7-8.5 carefully to the center of the membrane and allow to stand for 1 min. Centrifuge to collect cDNA (yield ~ 80%). Place the MinElute column into a fresh tube B. Add MilliQ H_2O pH 7-8.5 to the center of the membrane and allow to stand for 1 min. Centrifuge at 13,000 rpm for 1 min to collect residual cDNA. Transfer 4.5 µl from tube B to tube A (final volume 14.5 µl).

For hybridization, the following procedure is used: Mix purified DIG sample with hybridization solution (DIG-labeled cDNA, filtered 20x SSC, filtered 2x SDS). Prepare a slide heating block. Preheat the hybridization chamber. Heat hybridization solution at 99° C for 2 min to denature cDNA. In the meantime, prepare the slide and a 24 x 24 mm coverslip. When ready, immediately centrifuge the hybridization solution briefly, put the slide into the chamber, pipet SSC into each of the two wells of the chamber, and apply the solution onto the slide at the edge of the spotted area avoiding bubble formation by using curved-edge fine forceps to set the coverslip in place. Close the chamber and immerse it in a 63°C waterbath. Incubate chambers overnight.

Transfer slides one at a time from the chamber to the Coplin jar containing Wash A and let the coverslip fall off by gently moving the slide vertically in the solution. Once the coverslip

is removed, transfer the slide quickly to the rack in the trough of Wash A. When all slides are on the rack, wash by vigorous agitation for 5 min at room temperature. Transfer the slides quickly to the rack in the second trough containing Wash B. Wash by vigorous agitation for 3 min at room temperature. Transfer the rack to the third trough containing Wash B and wash by vigorous agitation for 3 min at room temperature. Dry slides and store in a slide box until scanning.

The ScanArray Express (Perkin Elmer Life Sciences, Boston, MA) can be used to scan the slides. Alternatively, the Image Trak Eip-Fluorescence System (Perkin Elmer Life Sciences, Boston, MA) can be used for 96,384, or 1536 well plates.

In summary, hybridization methodology and kits for the detection, identification, and quantification of Wise-associated nucleic acid sequences in cells are set forth herein. Using these methods, Wise wild type and mutant nucleic acid sequences can be identified, characterized, and quantified. In addition, kits may be produced utilizing Wise-derived nucleic acid molecule standards, antibodies, and kit components as described in the above methodology.

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Thus, there has been shown and described novel methods and compositions related to Wise, Sost, and LRP, which influence ocular development, bone deposition, Wnt pathway, and tooth development, which fulfills all the objects and advantages sought therefore. It is apparent to those skilled in the art, however, that many changes, variations, modifications, and other uses and applications for the subject methods and compositions are possible, and also such changes, variations, modifications, and other uses and applications which do not depart from the spirit and scope of the invention are deemed to be covered by the invention, which is limited only by the claims which follow.

What is claimed is:

1. A family of isolated nucleic acid molecules which can influence at least one of the following: tooth development, Wnt pathway activation, bone deposition, or ocular development, wherein the family is selected from the group consisting of:

(a) isolated nucleic acid molecule selected from the group consisting of SEQ ID NOs 1-8, 10-28, 96, 97, 108 – 111, 126, and 127, and complementary sequences thereof;

(b) degenerate variants of the sequences of step a;

(c) an isolated nucleic acid molecule that expresses a cysteine knot protein; and,

(d) oligonucleotide fragments which are 70% homologous to Exon 2 of SEQ. ID. NO. 128.

2. The isolated nucleic acid molecule of Claim 1(c), wherein the nucleic acid molecule is selected from the group consisting of Wise and Sost family member nucleic acid sequence molecules.

3. The isolated nucleic acid molecule of Claim 1, wherein nucleic acid molecules are homologous to the sequences of Claim 1, and are selected from the group consisting of genes, mRNA, cDNA, gDNA, tRNA, RNAi, SiRNA, oligonucleotides, polynucleotides, and nucleic acid sequence fragments.

4. The isolated nucleic acid molecules of Claim 1 wherein the molecules comprise genes, mRNA, cDNA, gDNA, tRNA, RNAi, oligonucleotides, polynucleotides, and nucleic acid sequence fragments.

5. Antisense RNAs complementary to at least one of the isolated nucleic acid molecules of Claim 1.

6. Mutations of the nucleic acid sequences of Claim 1, wherein mutants are selected from the group consisting of point, frame shift, deletion, and loss of function mutations.

7. The mutations of Claim 5 wherein the loss of function mutation comprises a stop codon associated with Exon1 of the Wise gene.

8. The mutations of Claim 5, wherein the loss of function mutation comprises a stop codon associated with the Sost gene.

9. An antisense oligonucleotide to any mRNA transcribed from at least one nucleic acid molecule of Claim 1.

10. An RNAi complementary to at least one of the nucleic acid sequences of Claim 1.

11. RNA nucleic acid molecules transcribed from the nucleic acid sequences of Claim 1.

12. A probe which hybridizes to at least one of the nucleic acid molecules of Claim 1 selected from the group consisting of cDNA and RNA labeled probes.

13. A vector comprising a promoter operably linked to a nucleic acid molecule according to Claim 1 or 6.

14. The vector of Claim 13, wherein the vector is selected from the group consisting of expression, cloning, and viral vectors.

15. The vector of Claim 13, wherein the vector is selected from the group consisting of expression vectors, fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-hybrid vectors, sequencing vectors, and cloning vectors.

16. The vector of Claim 13, wherein the vector is selected from the group consisting of prokaryotic and eukaryotic vectors.

17. The prokaryotic vector of Claim 16, wherein the vector is selected from the group consisting of pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280, pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT.

18. The eukaryotic vector of Claim 16, wherein the vector is selected from the group consisting of pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo, pSVK3, pSVL, pMSG, pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis.

19. The promoter of Claim 13, wherein the promotor is selected from the group consisting of a viral promoter and a cellular promoter.

20. The vector of Claim 13, wherein the vector comprises a selectable marker selected from the group consisting of an antibiotic resistance gene, a tRNA gene, an auxotrophic gene, a toxic gene, a phenotypic marker, a colorimetric marker, an antisense oligonucleotide, a restriction endonuclease, an enzyme cleavage site, a protein binding site, and an immunoglobulin binding site.

21. The vector of Claim 20, wherein the selectable marker is selected from the group consisting of LacZ, neo, Fc, DIG, myc, and FLAG.

22. The isolated nucleic acid molecule of Claim 1, wherein nucleic acid molecules homologous to the sequences of Claim 1 are selected from the group consisting of wild type, mutant, antisense, base-substituted, frame shift, deletion, and truncated genes.

23. The prokaryotic vector of Claim 17, wherein the vector replicates in a prokaryotic host cell selected from the group consisting of Gram-negative and Gram-positive bacterium.

24. The prokaryotic host cell of Claim 23, wherein the host cell is a bacterium selected from the group consisting of Escherichia, Salmonella, Proteus, Clostridium, Klebsiella, Bacillus, Streptomyces, and Pseudomonas.

25. The Gram-negative bacterium of Claim 23, wherein the bacterium is Escherichia coli.

26. The eukaryotic vector of Claim 16, wherein the vector replicates in a eukaryotic host cell selected from the group consisting of yeast, plant, fish, mammalian, human, mouse, frog, or insect cells.

27. The eukaryotic host cell of Claim 26, wherein the host cell is selected from cells of the group consisting of ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, and human or mammalian bone marrow stroma.

28. A host cell transfected with a vector according to Claim 13.

29. A morpholino antisense oligo molecule derived from any of the nucleic acid sequences of Claim 1.

30. The morpholino of Claim 29, wherein the effective amount of morpholino antisense oligo is within a concentration range between 0.1 nM to 10 mM.

31. A mutant Wise nucleic acid molecule selected from the group consisting of mutants of the following sequences:

(a) isolated nucleic acid molecule selected from the group consisting of SEQ. ID. NOs. 1-5, 96, 97, 109, 126-128, and complementary sequences thereof;

(b) degenerate variants of the sequences of step a;

(c) an isolated nucleic acid molecule that expresses a cysteine knot protein; and,

(d) oligonucleotide fragments which are 70% homologous to Exon 2 of SEQ. ID. NO. 128.

32. The mutant nucleic acid sequences of Claim 31, wherein mutants are selected from the group consisting of point, frame shift, deletion, and loss of function mutations.

33. A recombinant Wise plasmid formed from a mutant of Claim 31, a promoter, and a selectable marker.

34. The plasmid of Claim 33 comprising at least one stop codon.

35. A host cell transfected with the plasmid of Claim 33, wherein the host cell comprises stem cells.

36. A host cell transfected with the plasmid of Claim 33, wherein the host cell comprises embryonic cells.

37. A chimeric mammal wherein the host cell of Claim 35 or Claim 36 is used to transfect the mammal.

38. The transfected mammal of Claim 37, wherein a mouse is selected.

39. The promoter of Claim 33, wherein the promotor is selected from the group consisting of a viral promoter and a cellular promoter.

40. The Wise plasmid of Claim 33, wherein the selectable marker comprises at least one marker selected from the group consisting of an antibiotic resistance gene, a tRNA gene, an auxotrophic gene, a toxic gene, a phenotypic marker, a colorimetric marker, an antisense oligonucleotide, a restriction endonuclease, an enzyme cleavage site, an enzyme, a protein binding site, and an immunoglobulin binding site.

41. The Wise plasmid of Claim 33, wherein the selectable marker is selected from the group consisting of LacZ, neo, Fc, DIG, myc, and FLAG.

42. The Wise mutant nucleic acid molecule of Claim 31, wherein the sequences are selected from the group consisting of wild type, mutant, antisense, base-substituted, deletion, frameshift, and truncated genes.

43. The vector of Claim 33, wherein the vector is selected from the group consisting of prokaryotic and eukaryotic vectors.

44. A prokaryotic plasmid of Claim 43, wherein the plasmid replicates in a prokaryotic host cell selected from the group consisting of Gram-negative and Gram-positive bacterium.

45. A prokaryotic host cell transfected with the plasmid of Claim 33, wherein the host cell is selected from the group consisting of Escherichia, Salmonella, Proteus, Clostridium, Klebsiella, Bacillus, Streptomyces, and Pseudomonas.

46. The Gram-negative bacterium of Claim 43, wherein the bacterium is Escherichia coli.

47. A eukaryotic host cell transfected with the plasmid of Claim 33, wherein the plasmid replicates in a eukaryotic host cell selected from the group consisting of yeast, plant, fish, mammalian, human, frog, or insect cells.

48. The eukaryotic host cell of Claim 47, wherein the host cell is selected from cells of the group consisting of ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, and human or mammalian bone marrow stroma.

49. A mutant Wise nucleic acid molecule which can influence at least one of the following: tooth development, Wnt pathway, bone deposition, and ocular development selected from the group consisting of:

(a) mutants of isolated nucleic acid molecules comprising SEQ. ID. NOs. 1-5, 8, 109, 126 – 128, and complementary sequences thereof;

(b) degenerate variants of the sequences of step a; and,

(c) Wise nucleic acid molecules having a stop codon which prevents translation to a polypeptide.

50. A mutant Sost isolated nucleic acid molecule which can influence at least one of the following: tooth development, Wnt pathway, bone deposition, and ocular development selected from the group consisting of mutant variants of:

(a) Mutants of isolated nucleic acid molecule comprising SEQ. ID. NOs. 6, 7, 9 – 14, 110, and 111, and complementary sequences thereof; and,

(b) degenerate variants of the sequences of step a.

51. The isolated nucleic acid molecule of Claim 50, wherein nucleic acid molecules are homologous to the sequences of Claim 50, and are selected from the group consisting of genes, mRNA, cDNA, gDNA, tRNA, RNAi, oligonucleotides, polynucleotides, and nucleic acid sequence fragments.

52. The mutants of Claim 50, wherein the mutants comprise antisense RNAs complementary to the non-mutant isolated nucleic acid molecules.

53. The mutants of Claim 50, wherein mutants are selected from the group consisting of point, frame shift, deletion, and loss of function mutations.

54. The mutations of Claim 53, wherein the loss of function mutation comprises a stop codon at the start of the Sost gene.

55. An antisense oligonucleotide to any mRNA translated from a nucleic acid molecule of Claim 50.

56. An RNAi complementary to the non-mutant nucleic acid sequences homologous to the sequences of Claim 50.

57. RNA nucleic acid molecules transcribed from the nucleic acid sequences of Claim 50.

58. A probe which hybridizes to at least one of the nucleic acid molecules of Claim 50 selected from the group consisting of cDNA and RNA labeled probes.

59. A vector comprising a promoter operably linked to a nucleic acid molecule according to Claim 50.

60. The vector of Claim 59, wherein the vector is selected from the group consisting of expression, cloning, and viral vectors.

61. The vector of Claim 59, wherein the vector is selected from the group consisting of expression vectors, fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-hybrid vectors, sequencing vectors, and cloning vectors.

62. The vector of Claim 59, wherein the vector is selected from the group consisting of prokaryotic and eukaryotic vectors.

63. The prokaryotic vector of Claim 62, wherein the vector is selected from the group consisting of pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280, pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT.

64. The eukaryotic vector of Claim 62 wherein the vector is selected from the group consisting of pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo, pSVK3, pSVL, pMSG,

pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis.

65. The promoter of Claim 59, wherein the promotor is selected from the group consisting of a viral promoter and a cellular promoter.

66. The vector of Claim 59, wherein the vector comprises a selectable marker selected from the group consisting of an antibiotic resistance gene, a tRNA gene, an auxotrophic gene, a toxic gene, a phenotypic marker, a colorimetric marker, an antisense oligonucleotide, a restriction endonuclease, an enzyme cleavage site, a protein binding site, and an immunoglobulin binding site.

67. The vector of Claim 66, wherein the selectable marker is selected from the group consisting of LacZ, neo, Fc, DIG, myc, and FLAG.

68. The isolated nucleic acid molecule of Claim 50, wherein nucleic acid molecules homologous to the sequences of Claim 50 are selected from the group consisting of wild type, mutant, antisense, base-substituted, frame shift, deletion, and truncated genes.

69. The prokaryotic vector of Claim 63, wherein the vector replicates in a prokaryotic host cell selected from the group consisting of Gram-negative and Gram-positive bacterium.

70. The prokaryotic host cell of Claim 69, wherein the host cell is a bacterium selected from the group consisting of *Escherichia, Salmonella, Proteus, Clostridium, Klebsiella, Bacillus, Streptomyces,* and *Pseudomonas.*

71. The Gram-negative bacterium of Claim 69, wherein the bacterium is *Escherichia* coli.

72. The eukaryotic vector of Claim 64, wherein the vector replicates in a eukaryotic host cell selected from the group consisting of yeast, plant, fish, mammalian, human, mouse, frog, or insect cells.

73. The eukaryotic host cell of Claim 72, wherein the host cell is selected from cells of the group consisting of ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, and human or mammalian bone marrow stroma.

74. A host cell transfected with a vector according to Claim 59.

75. A morpholino antisense oligo molecule derived from the nucleic acid sequences of Claim 50.

76. The morpholino of Claim 75, wherein the effective amount of morpholino antisense oligo is within a concentration range between 0.1 nM to 10 mM.

77. A mutant LRP nucleic acid molecule which can influence at least one of the following: tooth development, Wnt pathway activation, bone deposition, or ocular development, selected from the group consisting of:

(a) mutants of isolated nucleic acid molecule selected from the group consisting of SEQ ID NOs 29 - 44, 99, 100, 112, 113, and complementary sequences thereof; and,

(b) degenerate variants of the sequences of step a.

78. The isolated nucleic acid molecule of Claim 77, wherein nucleic acid molecules are homologous to the sequences of Claim 77, and are selected from the group consisting of genes, mRNA, cDNA, gDNA, tRNA, RNAi, oligonucleotides, polynucleotides, and nucleic acid sequence fragments.

79. The mutants of Claim 77, wherein the mutants comprise antisense RNAs complementary to the isolated nucleic acid molecules of Claim 77.

80. The mutations of Claim 77, wherein mutants are selected from the group consisting of point, frame shift, deletion, and loss of function mutations.

81. An antisense oligonucleotide to any mRNA translated from a nucleic acid molecule of Claim 77.

82. An RNAi complementary to the nucleic acid sequences homologous to the sequences of Claim 77.

83. RNA nucleic acid molecules transcribed from the nucleic acid sequences of Claim 77.

84. A probe which hybridizes to at least one of the nucleic acid molecules of Claim 77 selected from the group consisting of cDNA and RNA labeled probes.

85. A vector comprising a promoter operably linked to a nucleic acid molecule according to Claim 77.

86. The vector of Claim 85, wherein the vector is selected from the group consisting of expression, cloning, and viral vectors.

87. The vector of Claim 85, wherein the vector is selected from the group consisting of expression vectors, fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-hybrid vectors, sequencing vectors, and cloning vectors.

88. The vector of Claim 85, wherein the vector is selected from the group consisting of prokaryotic and eukaryotic vectors.

89. The prokaryotic vector of Claim 88, wherein the vector is selected from the group consisting of pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280,

pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT.

90. The eukaryotic vector of Claim 88, wherein the vector is selected from the group consisting of pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo, pSVK3, pSVL, pMSG, pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis.

91. The promoter of Claim 85, wherein the promotor is selected from the group consisting of a viral promoter and a cellular promoter.

92. The vector of Claim 85, wherein the vector comprises a selectable marker selected from the group consisting of an antibiotic resistance gene, a tRNA gene, an auxotrophic gene, a toxic gene, a phenotypic marker, a colorimetric marker, an antisense oligonucleotide, a restriction endonuclease, an enzyme cleavage site, a protein binding site, and an immunoglobulin binding site.

93. The vector of Claim 91, wherein the selectable marker is selected from the group consisting of LacZ, neo, Fc, DIG, myc, and FLAG.

94. The isolated nucleic acid molecule of Claim 77, wherein nucleic acid molecules homologous to the sequences of Claim 77 are selected from the group consisting of wild type, mutant, antisense, base-substituted, frame shift, deletion, and truncated genes.

95. The prokaryotic vector of Claim 89, wherein the vector replicates in a prokaryotic host cell selected from the group consisting of Gram-negative and Gram-positive bacterium.

96. The prokaryotic host cell of Claim 95, wherein the host cell is a bacterium selected from the group consisting of *Escherichia, Salmonella, Proteus, Clostridium, Klebsiella, Bacillus, Streptomyces,* and *Pseudomonas*.

97. The Gram-negative bacterium of Claim 95, wherein the bacterium is *Escherichia coli*.

98. The eukaryotic vector of Claim 88, wherein the vector replicates in a eukaryotic host cell selected from the group consisting of yeast, plant, fish, mammalian, human, mouse, frog, or insect cells.

99. The eukaryotic host cell of Claim 97, wherein the host cell is selected from cells of the group consisting of ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, and human or mammalian bone marrow stroma.

100. A host cell transfected with a vector according to Claim 85.

101. A morpholino antisense oligo molecule derived from the nucleic acid sequences of Claim 77.

102. The morpholino of Claim 100, wherein the effective amount of morpholino antisense oligo is within a concentration range between 0.1 nM to 10 mM.

103. A mutant nucleic acid molecule, wherein the nucleic acid molecule is selected from the group consisting of mutagenized versions of LRP 1, 2, 5, and 6.

104. A nucleic acid sequence comprising a stop codon and a sequence selected from the group consisting of SEQ. ID. NOs. 1 – 44, 96 – 103, 108, 110 – 113, and 126 - 128.

105. A mutant of Wise SEQ. ID. NO. 126.

106. A mutant of mouse Wise nucleic acid SEQ. ID. NO. 1.

107. A mutant chick Wise protein SEQ. ID. NO. 4.

108. A mutant of Wise SEQ. ID. NO. 128.

109. A mutant of Wise SEQ. ID. NO. 2.

110. A mutant of Wise SEQ. ID. NO. 96.

111. A mutant of Wise SEQ. ID. NO. 97.

112. A mutant of Sost SEQ. ID. NO. 6.

113. A mutant of Sost SEQ. ID. NO. 8.

114. A mutant of Sost SEQ. ID. NO. 10.

115. A mutant of LRP SEQ. ID. NO. 38.

116. A mutant of LRP SEQ. ID. NO. 39.

117. A family of amino acid sequences which can influence at least one of the following: tooth development, Wnt pathway activation, bone deposition, or ocular development, selected from the group consisting of:

(a) an isolated amino acid sequence comprising SEQ ID NOs 45-48, 50-66, 104 – 107, 114 - 125;

(b) Wise amino acid sequences;

(c) Sost amino acid sequences;

(d) LRP amino acid sequences;

(e) an isolated amino acid sequence that is at least 70% homologous, to any of the proteins of (a); and,

(f) an isolated protein that has a cysteine knot formed from eight cysteine residues.

118. An antibody which binds to at least one of the amino acid sequences of Claim 117.

119. The antibodies of Claim 118, wherein the antibodies are selected from the group consisting of monoclonal antibody, polyclonal antibody, recombinant antibody, and antibody fragment.

120. A hybridoma cell that expresses at least one the antibodies of Claim 118.

121. An antibody that binds to a Wise polypeptide.

122. An antibody that binds to a Sost polypeptide.

123. An antibody that selectively binds to an epitope in the receptor-binding domain of the Wise protein.

124. The antibody of Claim 123, wherein an epitope on the Wise protein comprises a cysteine knot sequence that binds LRP, wherein the antibody prevents binding of the Wise protein to the LRP.

125. An Fab fragment derived from an antibody of Claim 118.

126. An anti-peptide antibody that prevents binding by Wise amino acid sequences to an LRP polypeptide selected from SEQ. ID. NOs. 67 - 95.

127. A Fab fragment that binds to any one of the polypeptides of Claim 117.

128. Fab fragments which bind to Exon 2 of Wise.

129. An anti-peptide antibody that prevents binding by Sost amino acid sequences to an LRP polypeptide selected from SEQ. ID. NOs. 67 - 95

130. A family of amino acid sequences selected from the group consisting of:

(a) an isolated amino acid sequence comprising SEQ ID NOS 45-53, 104 – 107, 114 - 125;

(b) Wise amino acid sequences; and,

(c) SOST amino acid sequences.

131. An antibody that binds to at least one of the amino acid sequences of Claim 130.

132. A Fab fragment from an antibody of Claim 131.

133. An isolated amino acid sequence selected from the group consisting of:

(a) an isolated amino acid sequence comprising SEQ ID NOS 45, 52, 104, 105, 106, 114 - 125;

(b) a Wise amino acid sequence encoded by any of the nucleic acid molecules of Claim 1; and,

(c) an isolated protein that has a cysteine knot formed from eight cysteine residues.

134. An antibody that binds to at least one of the amino acid sequences of Claim 133.

135. A Fab fragment from an antibody of Claim 134.

136. A family of amino acid sequences selected from the group consisting of:

(a) an isolated amino acid sequence comprising SEQ. ID. NOs. 46 – 51, 53, 109; and,

(b) a SOST amino acid sequence.

137. An antibody that binds to at least one of the amino acid sequences of Claim 136.

138. A Fab fragment from the antibody of Claim 137.

139. An anti-peptide antibody that prevents binding by a Sost amino acid sequences to an LRP polypeptide selected from SEQ. ID. NOs. 67 - 95.

140. An isolated amino acid sequence selected from the group consisting of:

(a) isolated amino acid sequences comprising SEQ. ID. NOs. 67 - 95;

(b) LRP polypeptides selected from the group consisting of LRP 1, 2, 5, and 6.

141. An antibody that binds to at least one of the amino acid sequences of Claim 140.

142. A Fab fragment from an antibody of Claim 141.

143. An isolated mutant amino acid sequence selected from the group consisting of:

(a) isolated mutagenized versions of amino acid sequences selected from SEQ. ID. NOs. 45 – 48, 50 – 66, 104 – 107, 114 - 125;

(b) mutagenized Wise amino acid sequences; and,

(c) mutagenized Sost amino acid sequences.

144. An antibody that binds to at least one of the amino acid sequences of Claim 143.

145. A Fab fragment from an antibody of Claim 144.

146. An isolated antibody derived from the group of polypeptides consisting of:

(a) an isolated amino acid sequence comprising SEQ. ID. NOs. 45 – 95, 104 – 107, and 114 - 125;

(b) anti-Wise antibodies;

(c) anti-Sost antibodies; and,

(d) LRP antibodies.

147. A host cell transfected invitro with an antibody of Claim 146.

148. A host cell transfected invivo with an antibody of Claim 146.

149. An Fab derived from one of the antibodies of Claim 146.

150. An Fab which prevents binding of Sost to LRP where in the Fab is derived from a Sost antibody.

151. An Fab which prevents binding of Wise to LRP when the Fab is derived from a Wise antibody.

152. A protein molecule comprising:

(a) a Wise polypeptide; and,

(b) an LRP polypeptide.

153. The protein of Claim 152, wherein the LRP polypeptide is selected from the group consisting of LRP 1, 2, 5, and 6 polypeptides.

154. A protein molecule comprising:

(a) a Sost polypeptide; and,

(b) an LRP polypeptide.

155. A method for increasing bone deposition, comprising:

(a) isolating a Wise nucleic acid sequence;

(b) attaching a stop codon at the beginning of the Wise nucleic acid sequence to form a Wise cassette;

(c) forming a Wise plasmid by inserting the Wise cassette into the plasmid;

(d) transfecting a host cell with the Wise plasmid, whereby homologous recombination occurs with a wild type Wise gene; and,

(e) activating the stop codon to cause a loss of function mutation.

156. The method of Claim 155, wherein the host cell is selected from the group consisting of an insect, an amphibian, and a non-human mammal.

157. The method of Claim 150, wherein the host cell is derived from a human.

158. The method of Claim 155, wherein expression is controlled by delivery of a Wise nucleic acid molecule into a host cell by a method selected from the group consisting of transfection, microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation.

159. The method of Claim 155, wherein the host cell is selected from the group consisting of osteoblasts and osteoclasts.

160. The method of Claim 155 comprising transfecting a host organism to form a chimeric host.

161. The method of Claim 160, wherein the chimeric host is a mouse.

162. The method of Claim 160, wherein the host cells are transfected *in vitro*.

163. A method for increasing bone deposition, comprising:

(a) isolating a Sost nucleic acid sequence;

(b) attaching a stop code at the beginning of the Sost nucleic acid sequence to form a Sost cassette;

(c) forming a Sost plasmid by inserting the Sost cassette into the plasmid;

(d) transfecting a host cell with the Sost plasmid, whereby homologous recombination occurs with a wild type Sost gene; and,

(e) activating the stop code to cause a loss of function mutation.

164. The method of Claim 163, wherein the host cell is selected from the group consisting of an insect, an amphibian, and a non-human mammal.

165. The method of Claim 163, wherein the host cell is derived from a human.

166. The method of Claim 163, wherein expression is controlled by delivery of a Wise nucleic acid molecule into a host cell by a method selected from the group consisting of microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation.

167. The method of Claim 163, wherein the host cell is selected from the group consisting of osteoblasts and osteoclasts.

168. The method of Claim 163 comprising transfecting a host organism to form a chimeric host.

169. The method of Claim 168, wherein the chimeric host is a mouse.

170. The method of Claim 163, wherein the host cells are transfected *in vitro*.

171. A method for increasing bone deposition, comprising:

(a) isolating a LRP nucleic acid sequence;

(b) attaching a stop code at the beginning of the LRP nucleic acid sequence to form an LRP cassette;

(c) forming an LRP plasmid by inserting the LRP cassette into the plasmid;

(d) transfecting a host cell with the LRP plasmid, whereby homologous recombination occurs with a wild type LRP gene; and,

(e) activating the stop code to cause a loss of function mutation.

172. The method of Claim 171, wherein the LRP is selected from the group consisting of LRP 1, 2, 5, and 6.

173. The method of Claim 171, wherein expression is controlled by delivery of an LRP nucleic acid molecule into a host cell by a method selected from the group consisting of transfection, microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation.

174. The method of Claim 171, wherein the host cell is selected from the group consisting of osteoblasts and osteoclasts.

175. The method of Claim 171 comprising transfecting a host organism to form a chimeric host.

176. The method of Claim 175, wherein the chimeric host is a mouse.

177. The method of Claim 171, wherein the host cells are transfected *in vitro*.

178. A method for affecting the Wnt pathway comprising:

(a) isolating a Wise nucleic acid sequence;

(b) attaching a stop code at the beginning of the Wise nucleic acid sequence to form a Wise cassette;

(c) forming a Wise plasmid by inserting the Wise cassette into the plasmid;

(d) transfecting a host cell with the Wise plasmid, whereby homologous recombination occurs with a wild type Wise gene; and,

(e) activating the stop code to cause a loss of function mutation.

179. A method for affecting the Wnt pathway comprising:

(a) isolating a Sost nucleic acid sequence;

(b) attaching a stop codon at the beginning of the Sost nucleic acid sequence to form a Sost cassette;

(c) forming a Sost plasmid by inserting the Sost cassette into the plasmid;

(d) transfecting a host cell with the Sost plasmid, whereby homologous recombination occurs with a wild type Sost gene; and,

(e) activating the stop code to cause a loss of function mutation.

180. A method for affecting the Wnt pathway comprising:

(a) isolating an LRP nucleic acid sequence;

(b) attaching a stop codon at the beginning of the LRP nucleic acid sequence to form an LRP cassette;

(c) forming an LRP plasmid by inserting the LRP cassette into the plasmid;

(d) transfecting a host cell with the LRP plasmid, whereby homologous recombination occurs with a wild type LRP gene; and,

(e) activating the stop code to cause a loss of function mutation.

181. A method for affecting tooth development comprising:

(a) isolating a Wise nucleic acid sequence;

(b) attaching a stop code at the beginning of the Wise nucleic acid sequence to form a Wise cassette;

(c) forming a Wise plasmid by inserting the Wise cassette into the plasmid;

(d) transfecting a host cell with the Wise plasmid, whereby homologous recombination occurs with a wild type Wise gene; and,

(e) activating the stop code to cause a loss of function mutation.

182. A method for affecting tooth development comprising:

(a) isolating a Sost nucleic acid sequence;

(b) attaching a stop code at the beginning of the Sost nucleic acid sequence to form a Sost cassette;

(c) forming a Sost plasmid by inserting the Sost cassette into the plasmid;

(d) transfecting a host cell with the Sost plasmid, whereby homologous recombination occurs with a wild type Sost gene; and,

(e) activating the stop code to cause a loss of function mutation.

183. A method for affecting tooth development comprising:

(a) isolating an LRP nucleic acid sequence;

(b) attaching a stop code at the beginning of the LRP nucleic acid sequence to form an LRP cassette;

(c) forming an LRP plasmid by inserting the LRP cassette into the plasmid;

(d) transfecting a host cell with the LRP plasmid, whereby homologous recombination occurs with a wild type LRP gene; and,

(e) activating the stop code to cause a loss of function mutation.

184. The method of Claim 183, wherein the plasmid includes a promoter.

185. The method of Claim 183, wherein the transfected host cell is delivered to a host organism to form a knockout host.

186. A method for predicting a defect in bone deposition, comprising:

(a) isolating a Wise gene;

(b) forming a labeled Wise gene probe; and,

(c) contacting the labeled gene probe with DNA from a homologue, whereby attachment of the labeled probe indicates a significant probability of normal bone development with normal activation of the Wnt pathway.

187. A method for causing increased bone deposition comprising:

(a) isolating a nucleic acid sequence selected from the group consisting of Wise, Sost, and LRP; and,

(b) forming an antisense RNA from the nucleic acid sequence;

(c) forming an antisense RNA vector; and,

(d) transfecting a host cell with the antisense RNA vector.

188. The method of Claim 187, wherein the host cell is selected from the group of animals consisting of insect, amphibian, and non-human mammal.

189. The method of Claim 187, wherein the host cell is from Homo sapiens.

190. The method of Claim 187, wherein expression is controlled by injection of an encoding nucleic acid molecule into an embryo.

191. The method of Claim 187, wherein the vector is inserted into a prenatal subject.

192. A method for increasing bone deposition comprising:

(a) isolating a Wise nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Wise nucleic acid sequence to produce Wise polypeptides;

(c) harvesting the Wise polypeptides;

(d) immunizing a host organism with the Wise polypeptides;

(e) isolating antibodies to the Wise polypeptides from the host;

(f) combining the antibodies with a carrier; and,

(g) transfecting a host cell *in vitro*.

193. The method of Claim 192, wherein a host organism is transfected with the carrier containing the antibodies.

194. The method of Claim 192, wherien the host cell is transfected *in vivo*.

195. The method of Claim 192, wherein expression is controlled by delivery of a Wise nucleic acid molecule into a host cell by a method selected from the group consisting of transfection, microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation.

196. The method of Claim 192, wherein the host cell is selected from the group consisting of osteoblasts and osteoclasts.

197. The method of Claim 192, wherein the antibodies are Fab fragments.

198. A method for increasing bone deposition comprising:

(a) isolating a Sost nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Sost nucleic acid sequence to produce Sost polypeptides;

(c) immunizing a host organism with the Sost polypeptides;

(d) isolating antibodies to the Sost polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vitro*.

199. A method for increasing bone deposition comprising:

(a) isolating an LRP nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the LRP nucleic acid sequence to produce LRP polypeptides;

(c) immunizing a host organism with the LRP polypeptides;

(d) isolating antibodies to the LRP polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vitro*.

200. A method for affecting the Wnt pathway comprising:

(a) isolating a Wise nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Wise nucleic acid sequence to produce Wise polypeptides;

(c) immunizing a host organism with the Wise polypeptides;

(d) isolating antibodies to the Wise polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vitro*.

201. A method for affecting the Wnt pathway comprising:

(a) isolating a Sost nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Sost nucleic acid sequence to produce Sost polypeptides;

(c) immunizing a host organism with the Sost polypeptides;

(d) isolating antibodies to the Sost polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vitro*.

202. A method for affecting the Wnt pathway comprising:

(a) isolating an LRP nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the LRP nucleic acid sequence to produce LRP polypeptides;

(c) immunizing a host organism with the LRP polypeptides;

(d) isolating Fab antibodies to the LRP polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vitro*.

203. A method for affecting tooth development comprising:

(a) isolating a nucleic acid sequence selected from the group consisting of Wise, Sost, and LRP;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the nucleic acid sequence to produce polypeptides;

(c) immunizing a host organism with the polypeptides;

(d) isolating antibodies to the polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vivo*.

204. A method for affecting ocular development comprising:

(a) isolating a nucleic acid sequence selected from the group consisting of Wise, Sost, and LRP;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the nucleic acid sequence to produce polypeptides;

(c) immunizing a host organism with the polypeptides;

(d) isolating antibodies to the polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vivo*.

205. A method for preventing Sost from binding to an LRP selected from the group consisting of LRP5 and LRP6 comprising:

(a) isolating a Sost nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Sost nucleic acid sequence to produce Sost polypeptides;

(c) immunizing a host organism with the Sost polypeptides;

(d) isolating antibodies to the LRP polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vivo*.

206. A method for preventing Wise from binding to an LRP selected from the group consisting of LRP5 and LRP6 comprising:

(a) isolating a Wise nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Wise nucleic acid sequence to produce Wise polypeptides;

(c) immunizing a host organism with the Wise polypeptides;

(d) isolating antibodies to the Wise polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vitro*.

207. A method for affecting either bone deposition, ocular development, Wnt pathway, or tooth development, comprising transfecting a host cell with an antibody derived from the group consisting of antibodies to LRP, Wise, and Sost, wherein the antibody prevents wild-type polypeptides from binding with their targets.

208. A kit for detecting a Wise polypeptide, wherein the kit comprises:

(a) a container; and,

(b) a Wise antibody with a marker.

209. A kit for detecting a Wise nucleic acid molecule, wherein the kit comprises:

(a) a container; and,

(b) a Wise probe.

210. The method of Claim 207, wherein the protein molecule is isolated from a host organism in the group selected from Humans, xenopus, frogs, and *Drosophila*.

211. A method for blocking Wise/SOST expression using a morpholino.

212. The kit of Claim 208, wherein the markers comprise en2, Krox20, Hoxb9, myosin, RT-PCR, Ef1-Δ, NCAM, otx2, myosin light chain, and muscle actin.

213. The method of Claim 208, wherein the markers are selected from the group consisting of posterior, midbrain, hindbrain, spinal cord, mesoderm, muscle, and neural markers.

214. A Wise nucleic acid sequence comprising Wise, hemaglutinin, myc, stop codon, and FLAG sequences.

215. A method for activating canonical Wnt signaling comprising:

(a) injecting a Wise protein into an embryo, wherein the Wise protein binds to a Frizzled receptor thereby inhibiting the binding of the Wnt protein to the Frizzled receptor; and,

(b) activating canonical Wnt signaling.

216. A family of nucleic acid sequences selected from the group consisting of Caronte, Wise, Sost Dan, Cereberus, Gremlin, CTGF, Soggy, DKK1, DKK2, DKK3, DKK4, NOV, mucin, slit, OH, WISP, and CCN.

217. A method for producing a Wise mutant mouse comprising:

(a) introducing a mutant Wise gene into a mouse embryonic stem cell;

(b) introducing the embryonic stem cell into a mouse blastocyst to create a transgenic embryo; and,

(c) allowing the embryo to develop into the Wise mouse.

218. The method of Claim 217, wherein the introduction of a gene into the stem cell is selected from the group of methods consisting of transfection, micro-injection, biolistic particle delivery, lipofection, and electroporation.

219. The method of Claim 217, wherein the Wise mouse exhibits developmental abnormalities selected from the group consisting of bone deposition, dental, neurological, and ocular abnormalities.

220. The mutated Wise gene of Claim 217, wherein the gene is selected from the group consisting of antisense, base-substituted, and truncated gene sequences.

221. An isolated mouse cell comprising a mutated Wise gene, wherein the endogenous wild type Wise gene has been replaced with the mutated Wise gene.

222. The mutated Wise gene of Claim 221, wherein the gene is selected from the group consisting of antisense, base-substituted, and truncated genes.

223. A Wise pET vector comprising a mutated Wise gene sequence, neo, and LacZ.

224. The mutated Wise sequence of Claim 223, wherein the gene sequence is selected from the group consisting of antisense, base-substituted, and truncated sequences.

225. A Sost pET vector comprising a mutated Sost sequence, neo, and LacZ.

226. The mutated Sost sequence of Claim 225, wherein the gene sequence is selected from the group consisting of antisense, base-substituted, and truncated sequences.

227. A mutant Wise mouse comprising the mutant Wise nucleic acid sequence of Claim 31.

228. The Wise mouse of Claim 227, wherein the mutant Wise gene is selected from the group consisting of homozygous and heterozygous genes.

229. A Sost mouse comprising the mutant Sost gene sequence of Claim 49.

230. The Sost mouse of Claim 229, wherein the mutant Sost gene is selected from the group consisting of homozygous and heterozygous genes.

231. A mutant Wise mouse made by the steps comprising:

(a) introducing a mutant Wise gene into a mouse embryonic stem cell;

(b) introducing the embryonic stem cell into a mouse blastocyst to create a transgenic embryo; and,

(c) allowing the embryo to develop into the mutant Wise mouse.

232. A family of nucleic acid sequences which can influence at least one of the following: bone deposition, Wnt pathway, tooth development, and ocular development, selected from the group consisting of SEQ. ID. NOs. 1 - 44.

233. An isolated nucleic acid sequence which regulates bone deposition, ocular development, Wnt pathway, and tooth development, and binds to LRP.

234. The isolated nucleic acid sequence of Claim 233, wherein the sequence is selected from the group consisting of Wise and Sost nucleic acid sequences.

235. A method for producing a transgenic mutant Wise mouse, comprising:

(a) microinjecting a Wise cassette containing a mutant Wise nucleic acid sequence into a blastomere;

(b) injecting the blastomere into a host mouse embryo; and,

(c) growing the embryo to maturation.

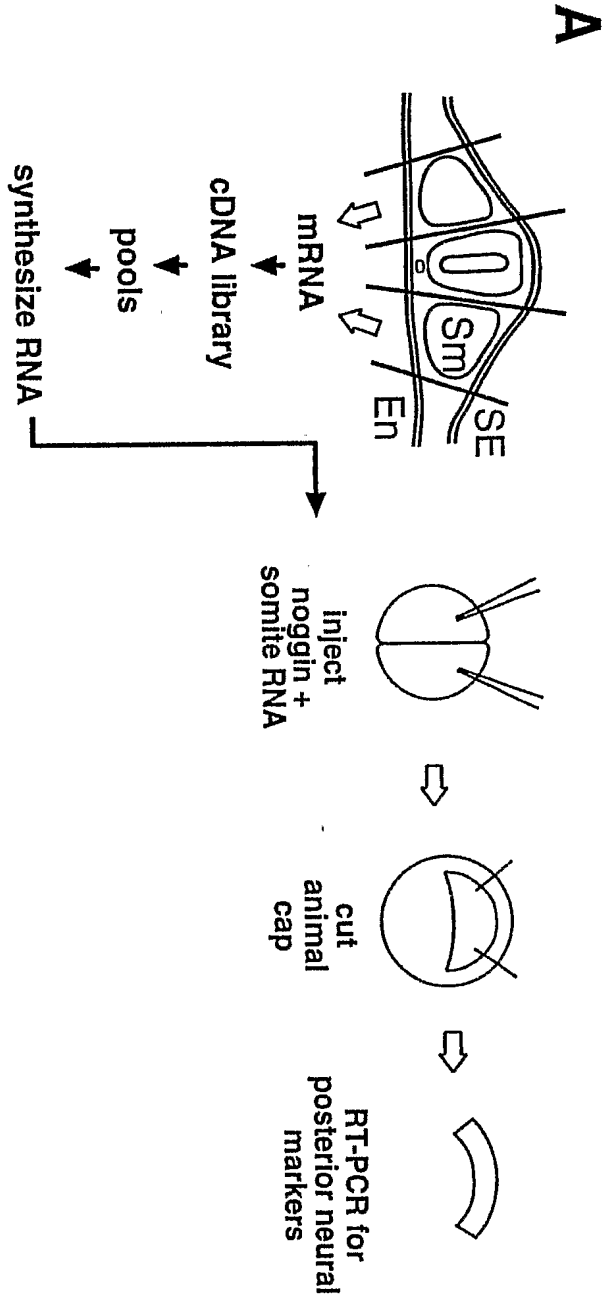

A
SE
En
Sm
D
mRNA
cDNA library
pools
synthesize RNA
inject noggin + somite RNA
cut animal cap
RT-PCR for posterior neural markers

Fig. 1A

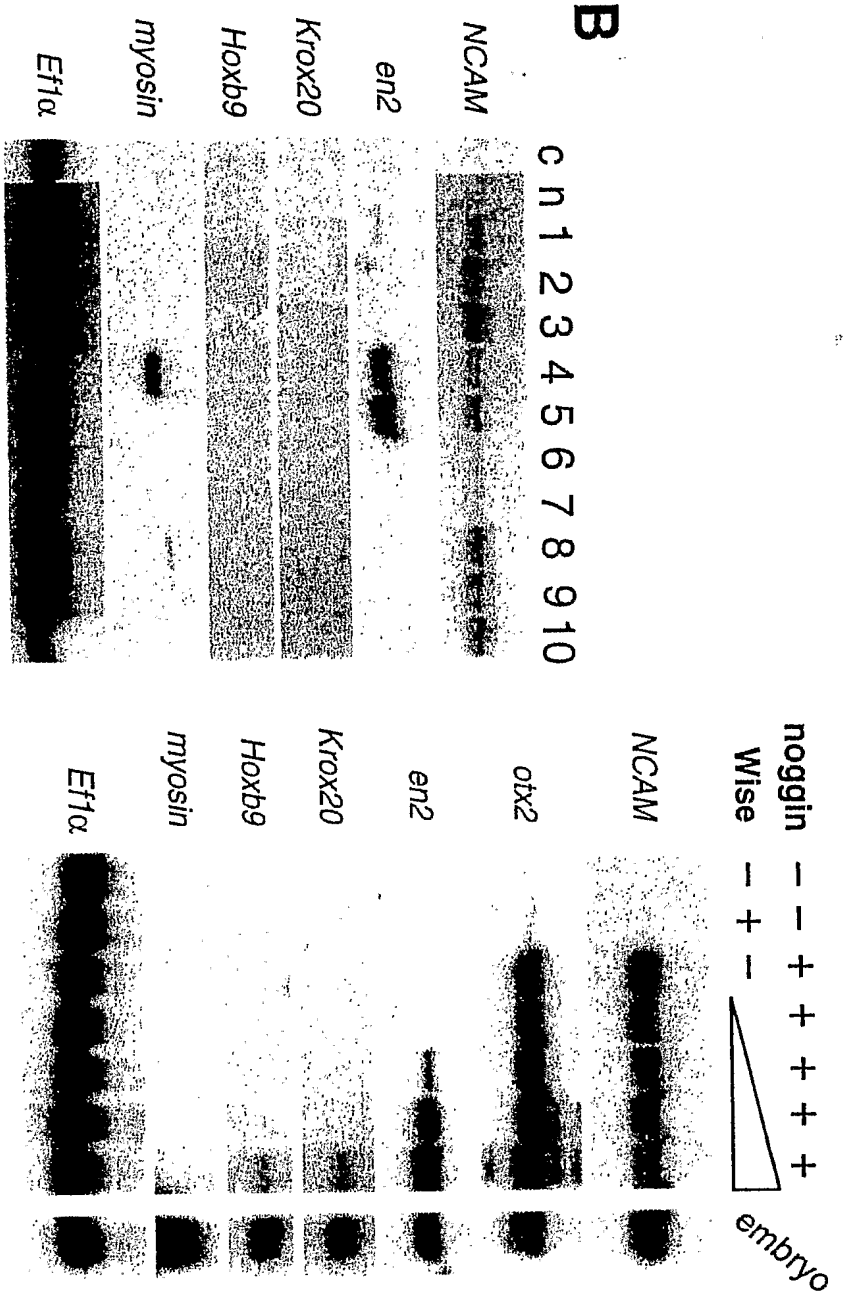

B
c n 1 2 3 4 5 6 7 8 9 10
NCAM
en2
Krox20
Hoxb9
myosin
Ef1α
C
noggin
Wise
NCAM
otx2
en2
Krox20
Hoxb9
myosin
Ef1α
embryo

Fig. 1B and C

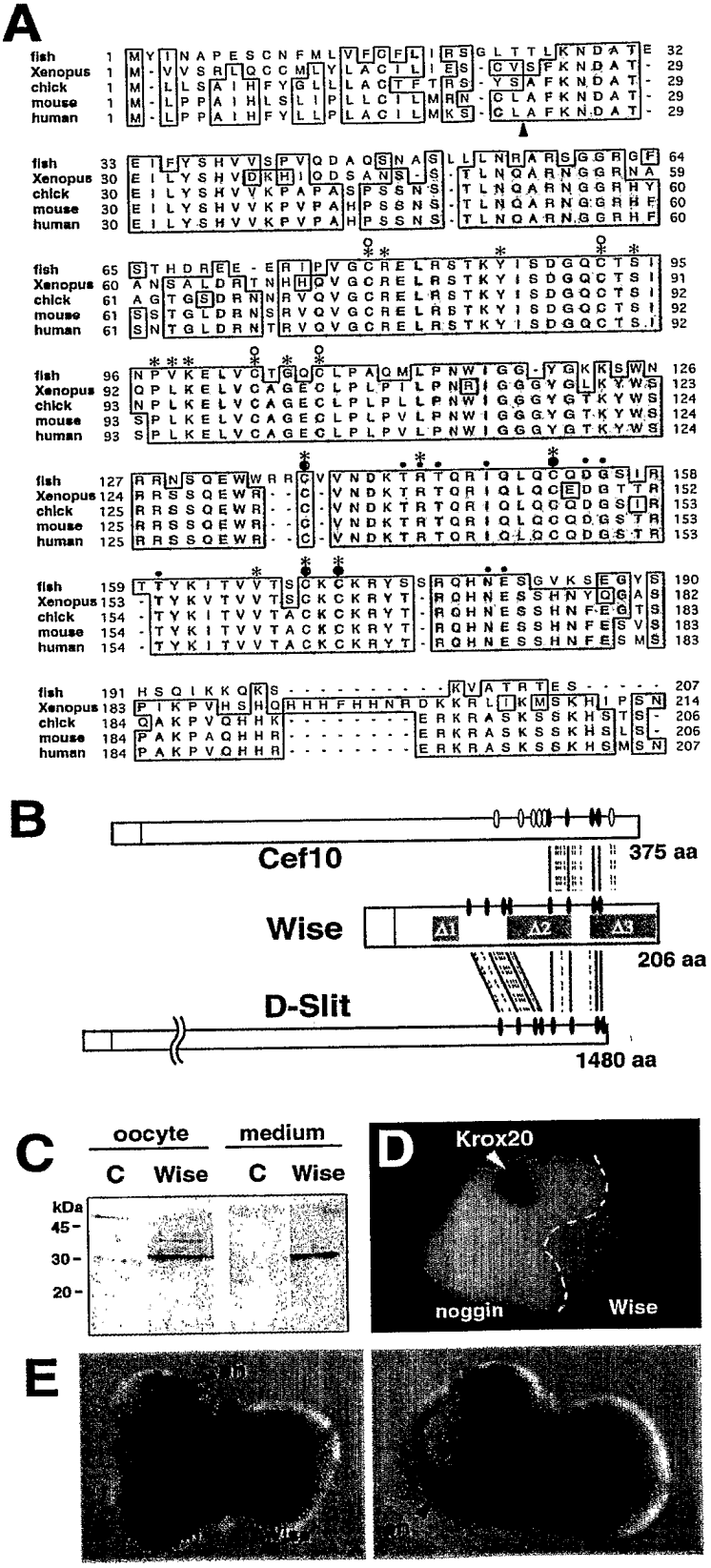

A
fish
Xenopus
chick
mouse
human
B
Cef10
375 aa
Wise
A1
A2
A3
206 aa
D-Slit
1480 aa
C
oocyte
medium
C
Wise
C
Wise
kDa
45-
30-
20-
D
Krox20
noggin
Wise
E

Fig 2

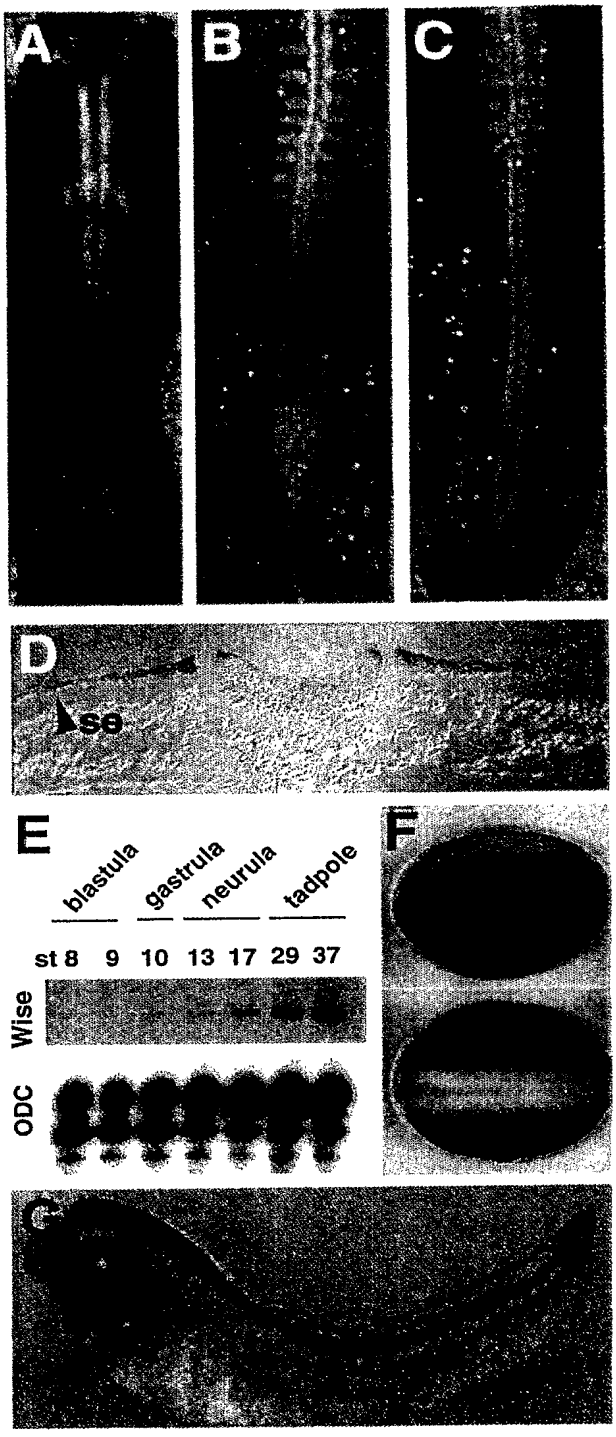

A
B
C
D
se
E
blastula
gastrula
neurula
tadpole
st 8 9 10 13 17 29 37
Wise
ODC
F
G

Fig 3

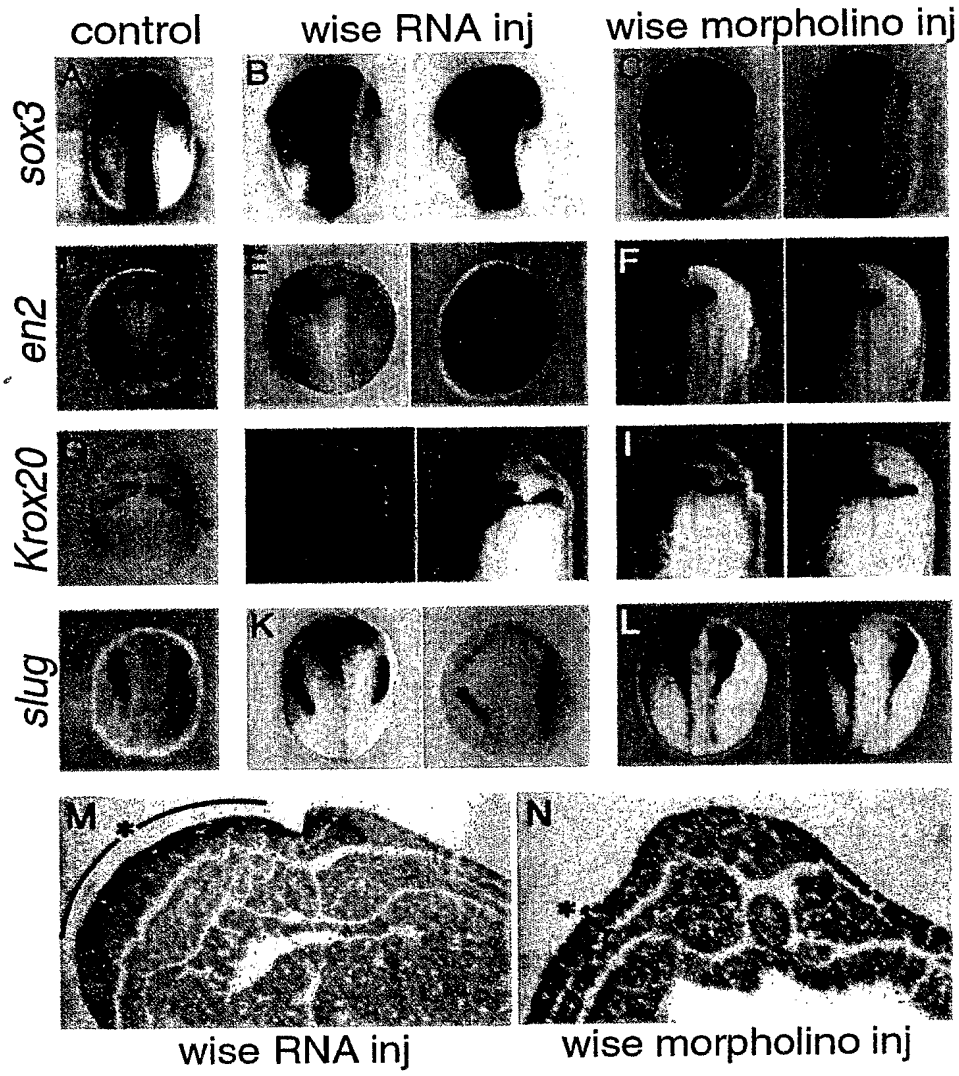

control
wise RNA inj
wise morpholino inj
sox3
en2
Krox20
slug
A
B
C
E
F
I
K
L
M
N
wise RNA inj
wise morpholino inj

Fig 4

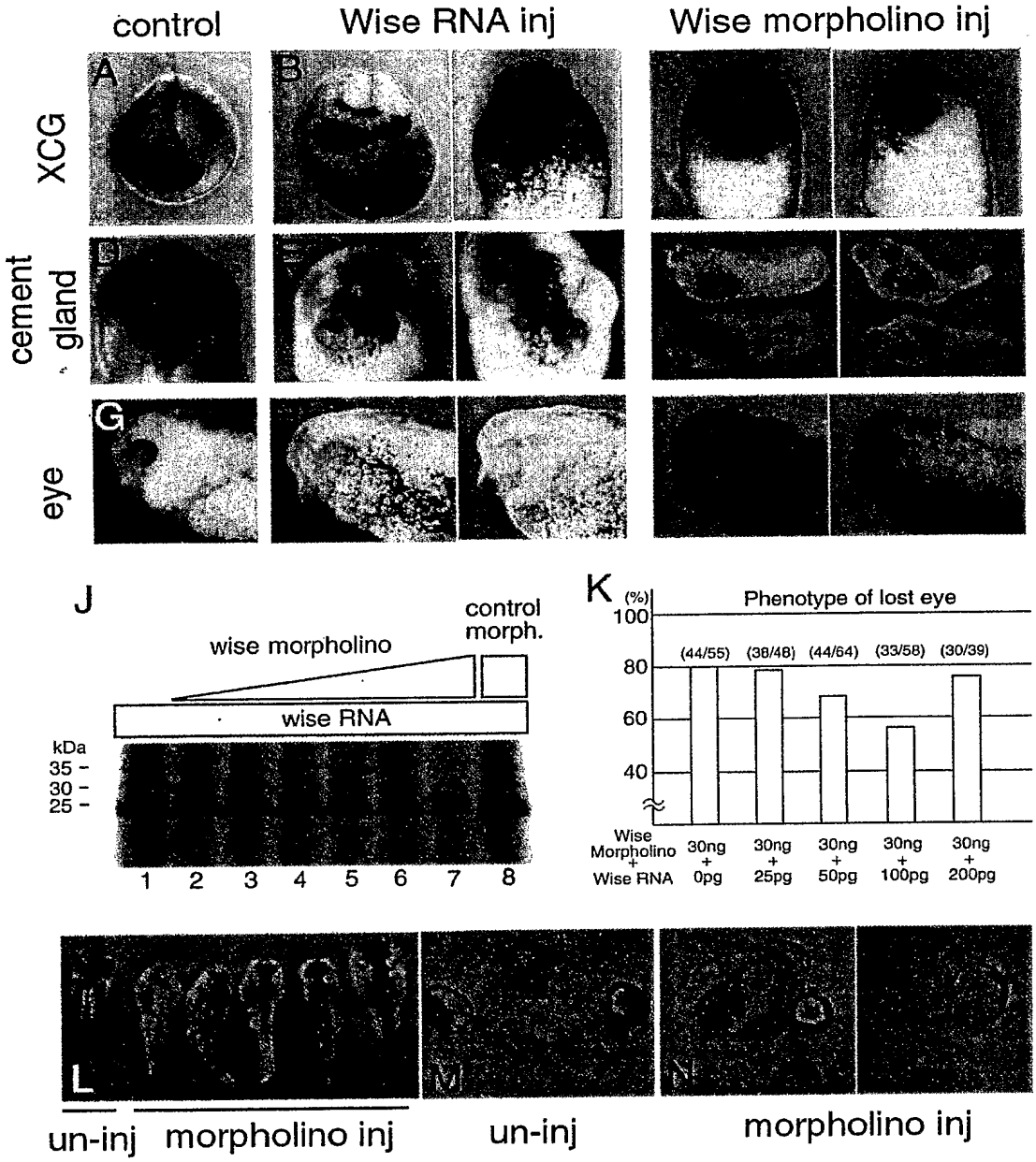

control
Wise RNA inj
Wise morpholino inj
XCG
cement gland
eye
A
B
G
J
control morph.
wise morpholino
wise RNA
kDa
35 –
30 –
25 –
1 2 3 4 5 6 7 8
K
(%)
Phenotype of lost eye
100
80
60
40
(44/55) (38/48) (44/64) (33/58) (30/39)
Wise Morpholino + Wise RNA
30ng + 0pg
30ng + 25pg
30ng + 50pg
30ng + 100pg
30ng + 200pg
L
M
N
un-inj
morpholino inj
un-inj
morpholino inj

Fig 5

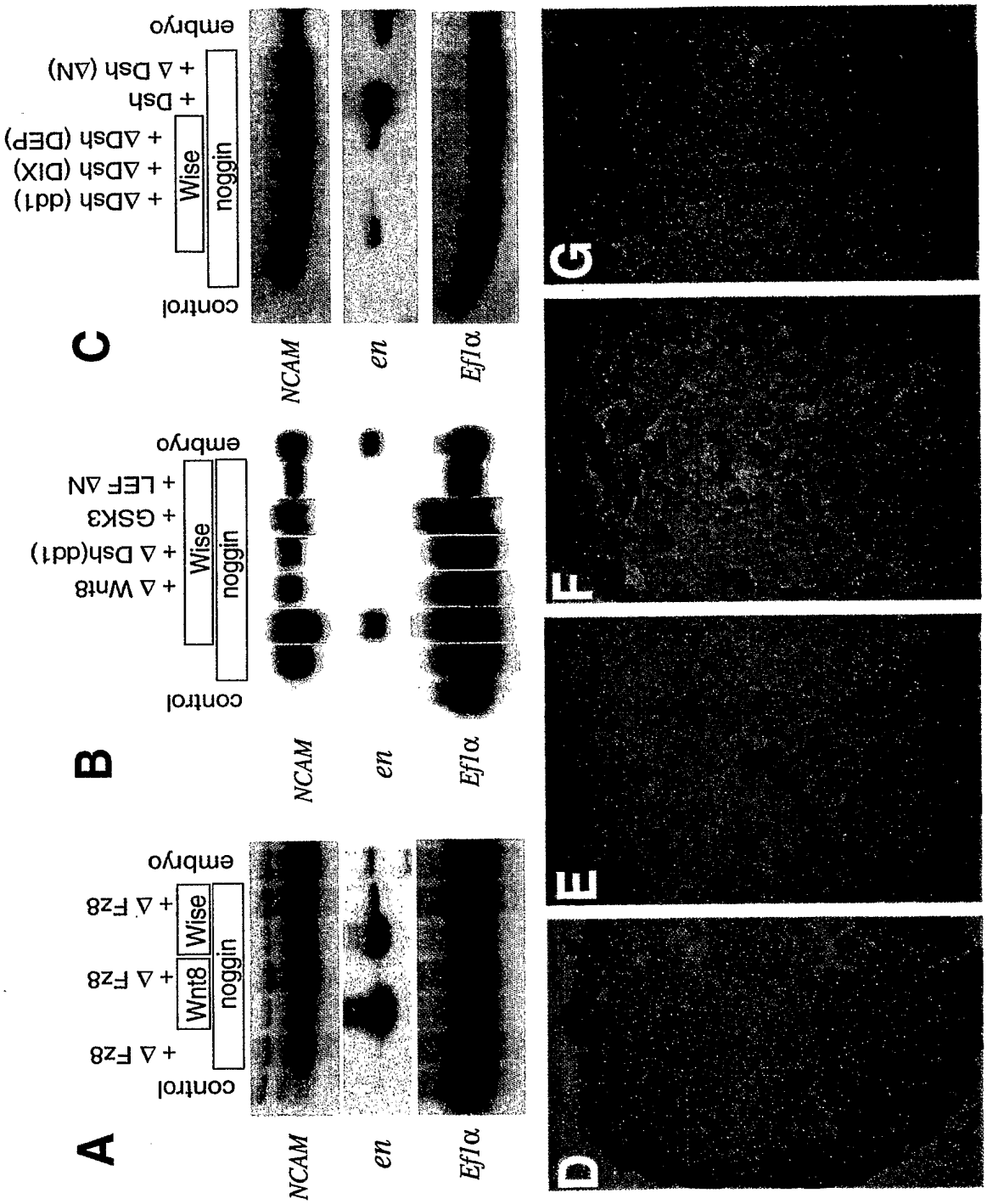

A
control
+ Δ Fz8
Wnt8
noggin
+ Δ Fz8
Wise
+ Δ Fz8
embryo
NCAM
en
Ef1α
B
control
noggin
Wise
+ Δ Wnt8
+ Δ Dsh(dd1)
+ GSK3
+ LEF ΔN
embryo
NCAM
en
Ef1α
C
control
noggin
Wise
+ ΔDsh (dd1)
+ ΔDsh (DIX)
+ ΔDsh (DEP)
+ Dsh
+ Δ Dsh (ΔN)
embryo
NCAM
en
Ef1α
D
E
F
G

Fig 6

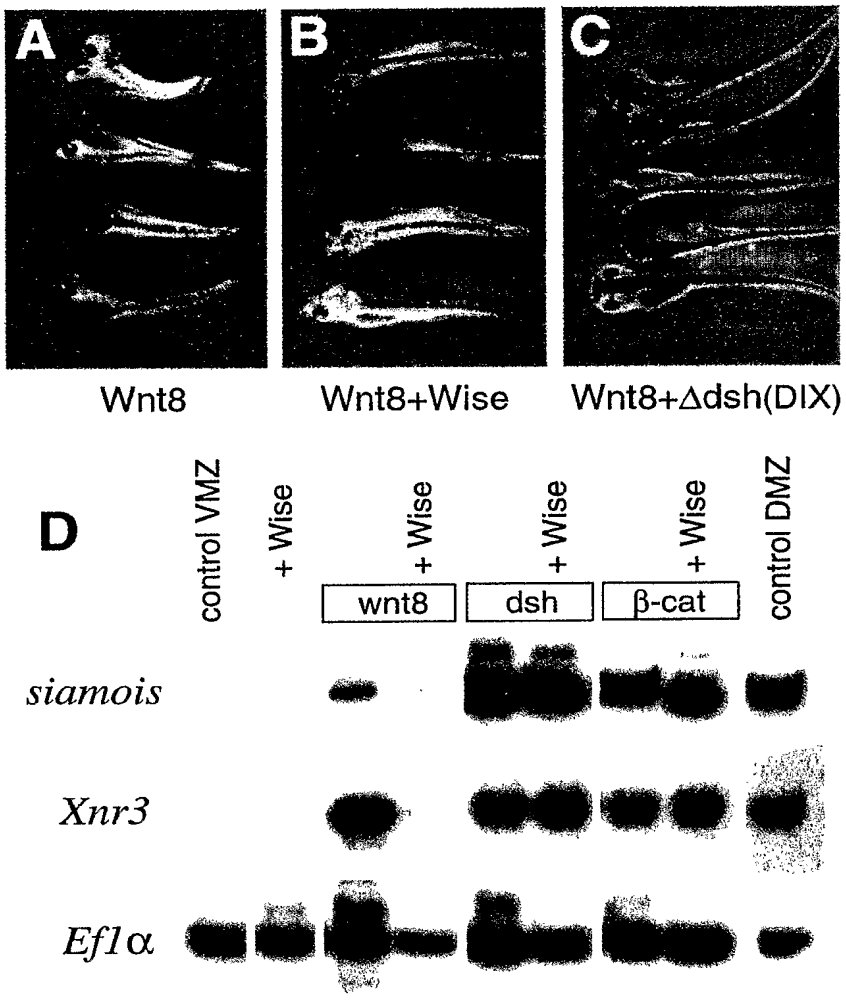

A
B
C
Wnt8
Wnt8+Wise
Wnt8+Δdsh(DIX)
D
control VMZ
+ Wise
+ Wise
+ Wise
+ Wise
control DMZ
wnt8
dsh
β-cat
siamois
Xnr3
Efl α

Fig. 7 A-D

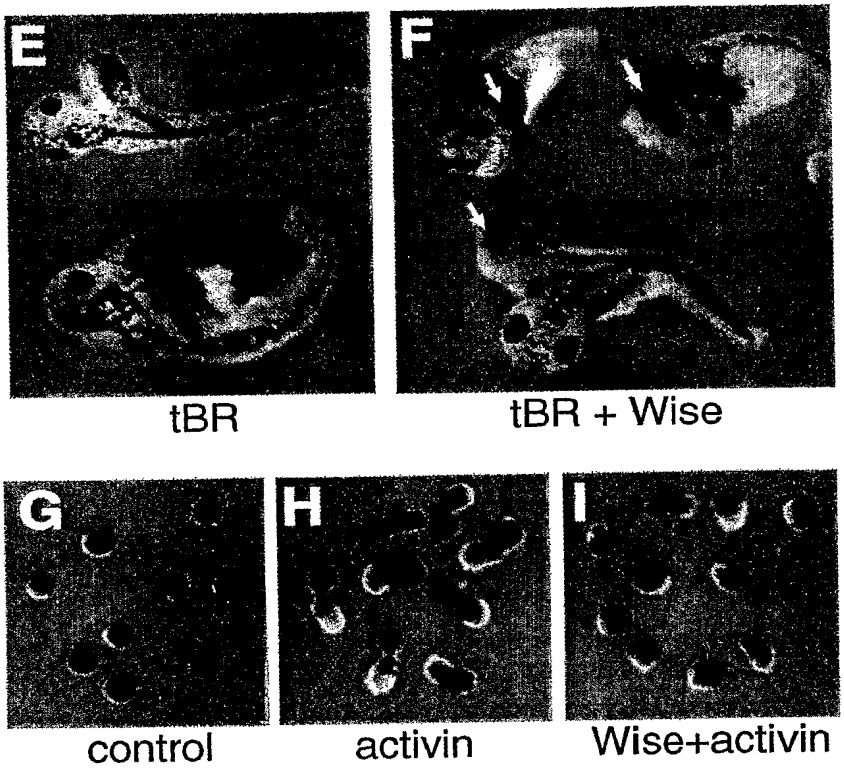
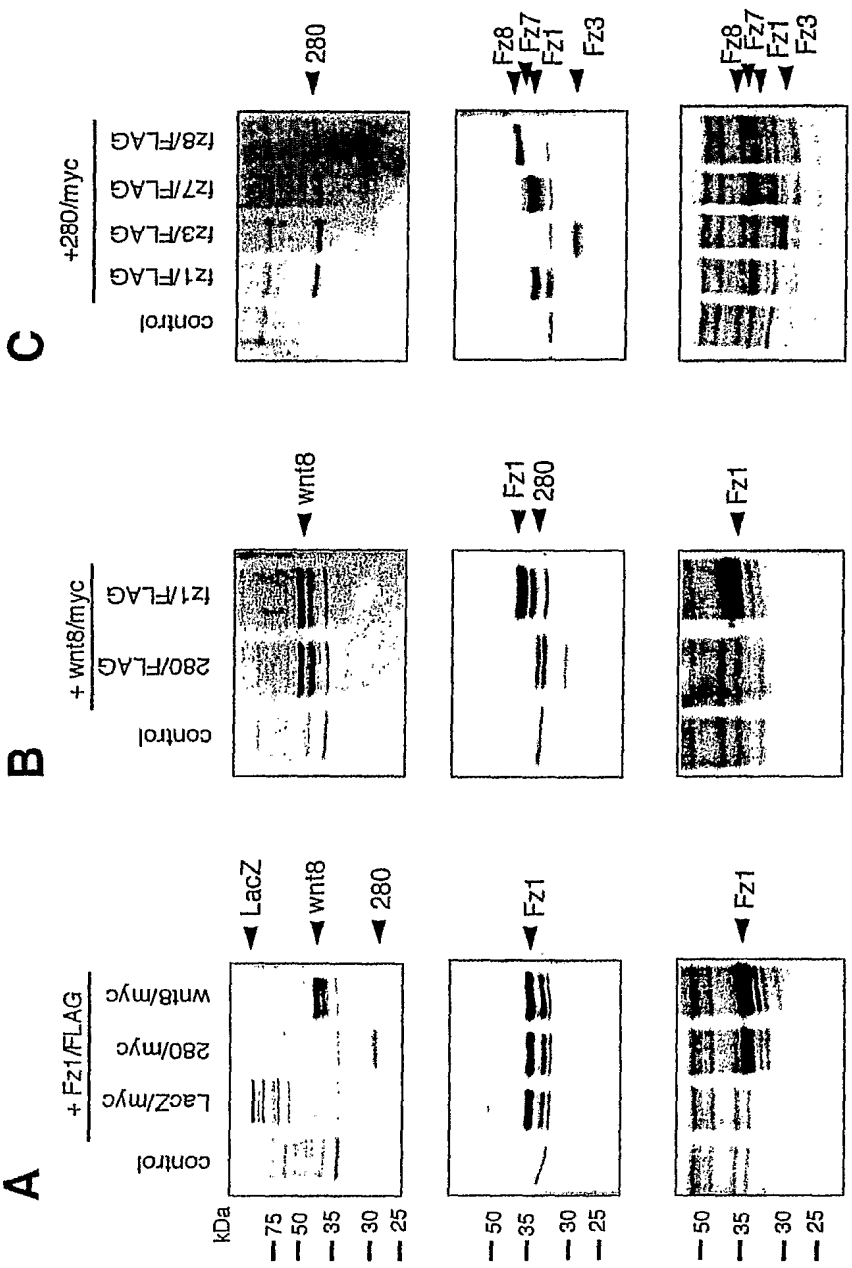


Fig. 7E - I


A
+ Fz1/FLAG
control
LacZ/myc
280/myc
wnt8/myc
LacZ
wnt8
280
Fz1
Fz1
kDa
75
50
35
30
25
50
35
30
25
50
35
30
25
cell extract
Western: anti-myc
cell extract
Western: anti-FLAG
IP with anti-myc
Western: anti-FLAG
B
+ wnt8/myc
control
280/FLAG
fz1/FLAG
wnt8
Fz1
280
Fz1
C
+280/myc
control
fz1/FLAG
fz3/FLAG
fz7/FLAG
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Fz8
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Fz3
Fz8
Fz7
Fz1
Fz3

Fig. 8

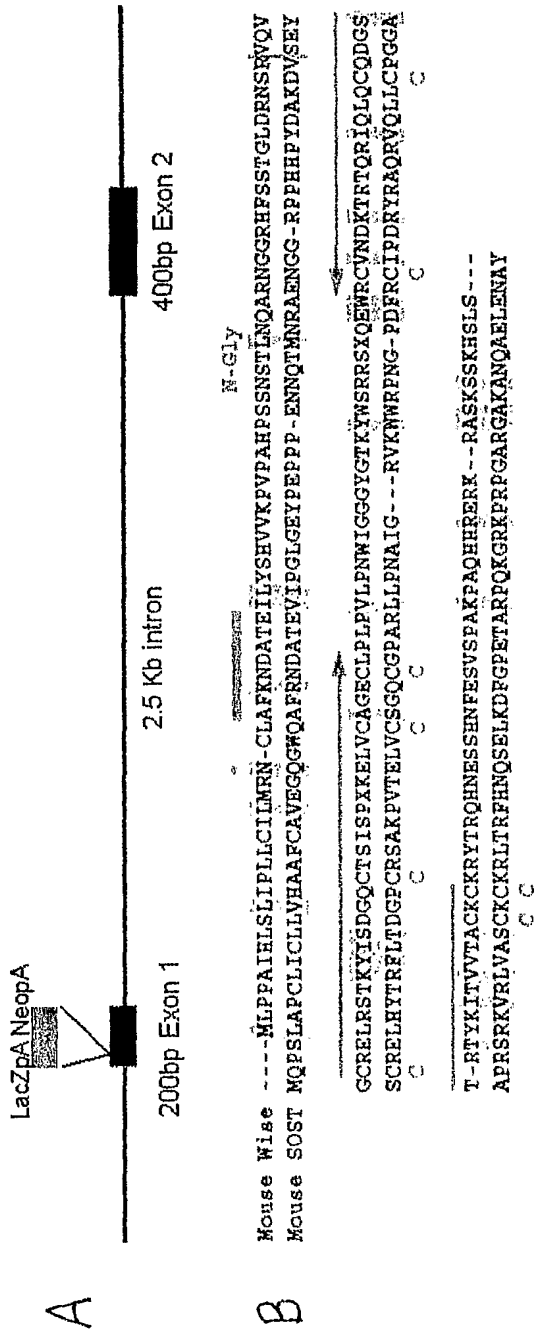
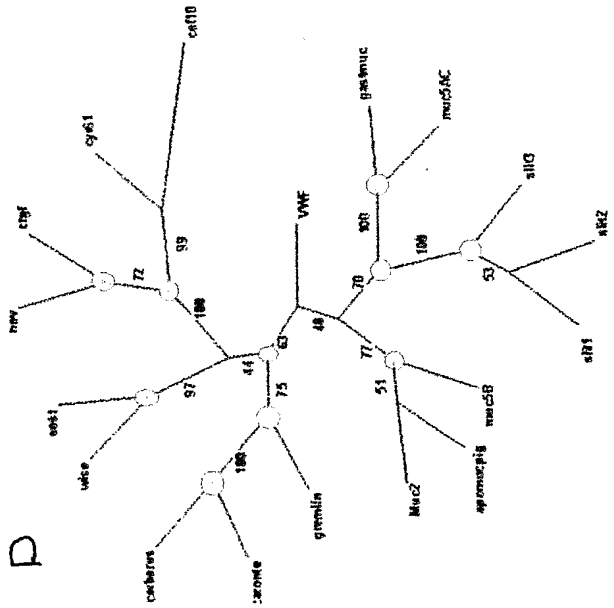

A
LacZpA NeopA
200bp Exon 1
2.5 Kb intron
400bp Exon 2
B
N-Gly
Mouse Wise ----MLPPAIELSLIPLLCTIMRN-CLAFKNDATEILYSHVVKPVPAHPSSNSTLNQARNGGRHFSSTGLDRNSRVQV
Mouse SOST MQPSLAPCLICLLVHAAFCAVEGQGMQAFNDATEVIPGLGEYPEPPP-ENNQTMNRAENGG-RPPHHPYDAKDVSEY
GCRELRSTKYISDGQCTSISPAKELVCAGECLPLPVLPNWIGGGYGTKYWSRRSXQEWRCVNDKTRTQRIQLQCQDGS
SCRELHYTRFLTDGPCRSAKPVTELVCSGQCGPARLLPNAIG---RVKNWRPNG-PDFRCIPDRYRAQRVQLLCPGGA
T-RTYKITVVTACKCKRYTRQHNESSHNFESVSPAKPAQHHRERK--RASKSSKHSLS---
APRSRKVRLVASCKCKRLTRFHNQSELKDFGPETARPQKGRKPRPGARGAKANQAELENAY

Fig. 9A and B


cat10
cyt61
ctgf
nov
vWF
gastmuc
muc5AC
sli03
slit2
slit1
99
72
100
100
70
53
48
63
44
77
97
75
51
sdd1
vdo
muc5B
Muc2
agrinscipin
gremlin
carbanyd
zonule
D

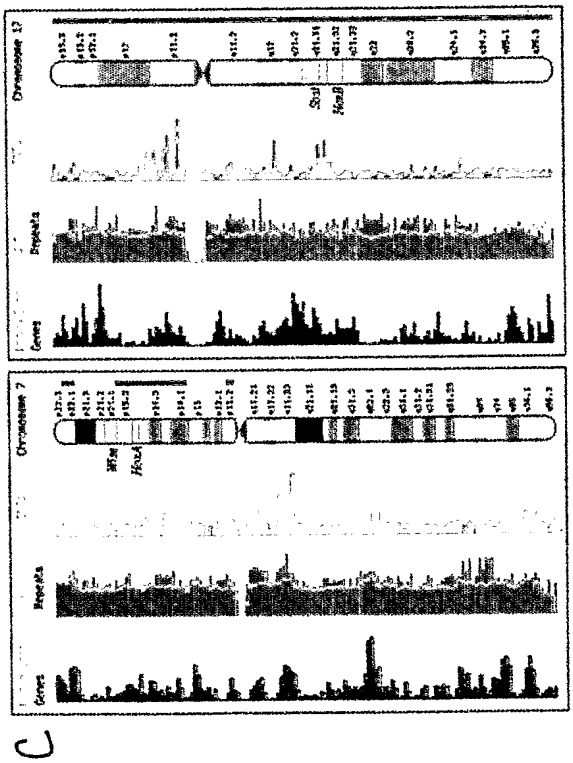
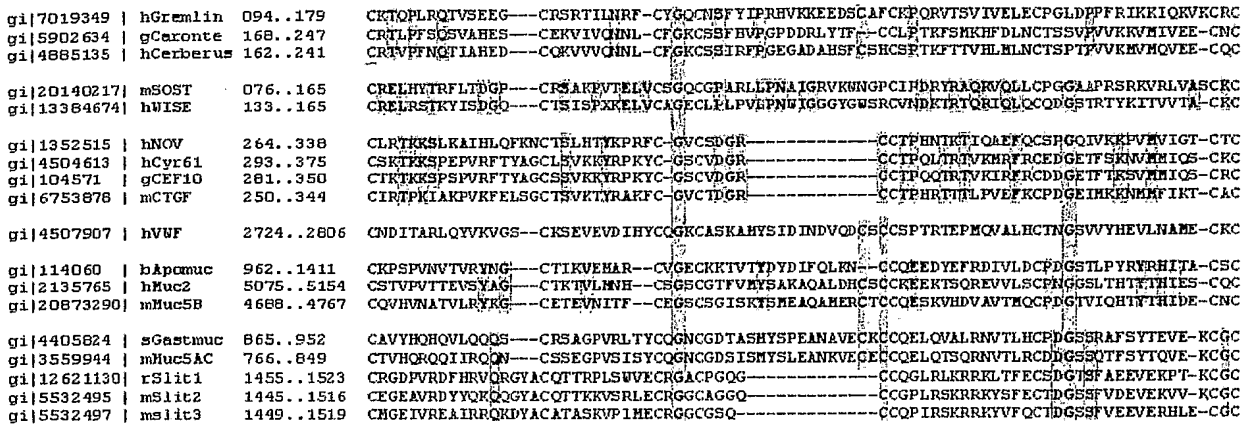

Chromosome 17
Chromosome 7
Repeats
Genes
C

Fig 9C and D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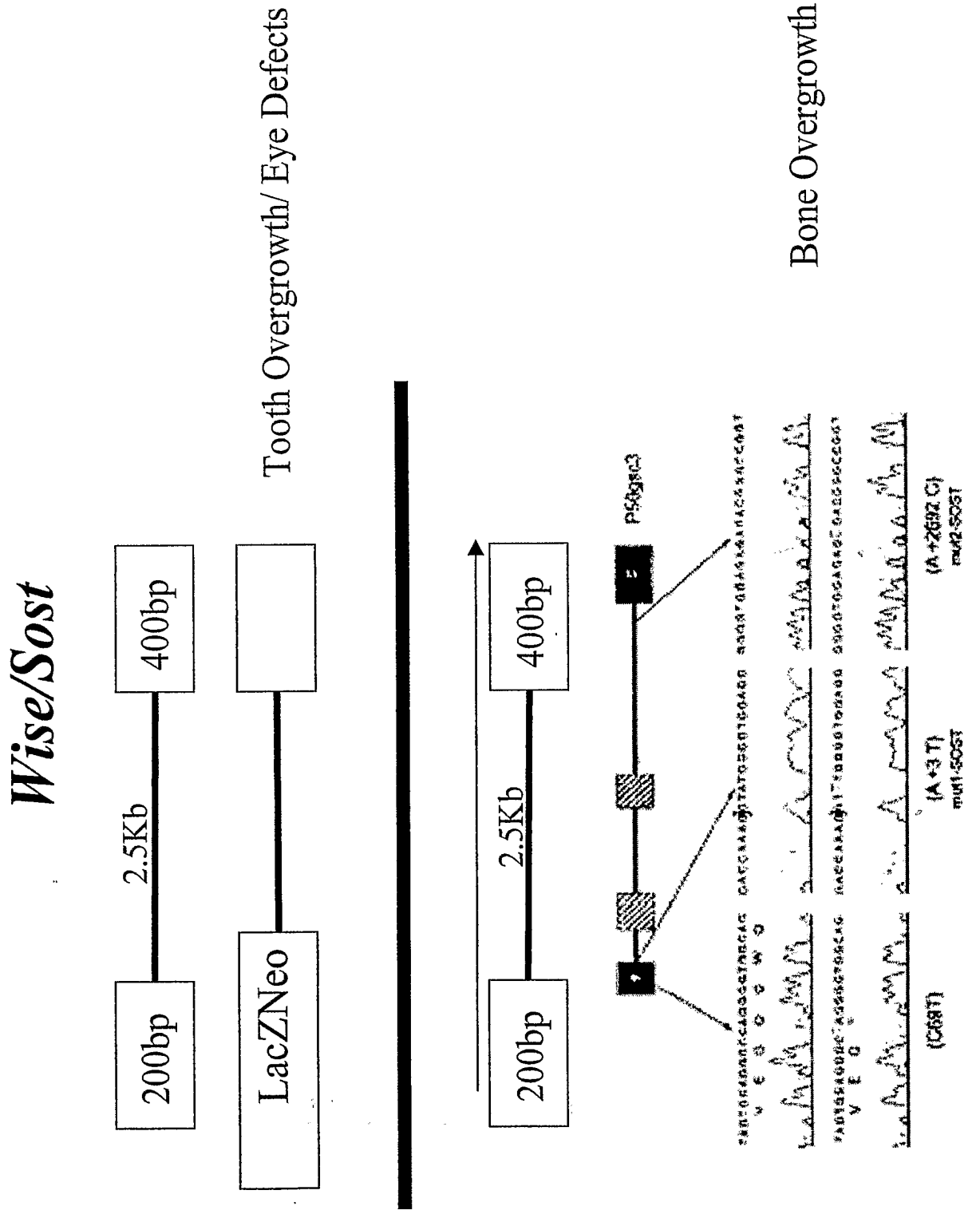
gi|5902634 | gCaronte 168..247
gi|4885135 | hCerberus 162..241
gi|20140217| mSOST 076..165
gi|13384674| hWISE 133..165
gi|1352515 | hNOV 264..338
gi|4504613 | hCyr61 293..375
gi|104571 | gCEF10 281..350
gi|6753878 | mCTGF 250..344
gi|4507907 | hVWF 2724..2806
gi|114060 | hApomuc 962..1411
gi|2135765 | hMuc2 5075..5154
gi|20873290| mMuc5B 4688..4767
gi|4405824 | sGastmuc 865..952
gi|3559944 | mMuc5AC 766..849
gi|12621130| rSlit1 1455..1523
gi|5532495 | mSlit2 1445..1516
gi|5532497 | mslit3 1449..1519

E

Fig. 9E

Fig. 10


Wise/Sost
2.5Kb
400bp
200bp
LacZNeo
Tooth Overgrowth/ Eye Defects
2.5Kb
400bp
200bp
Bone Overgrowth
P50gsc3
(C68T)
(A +3 T)
mut1-SOST
(A +2692 C)
mut2-SOST

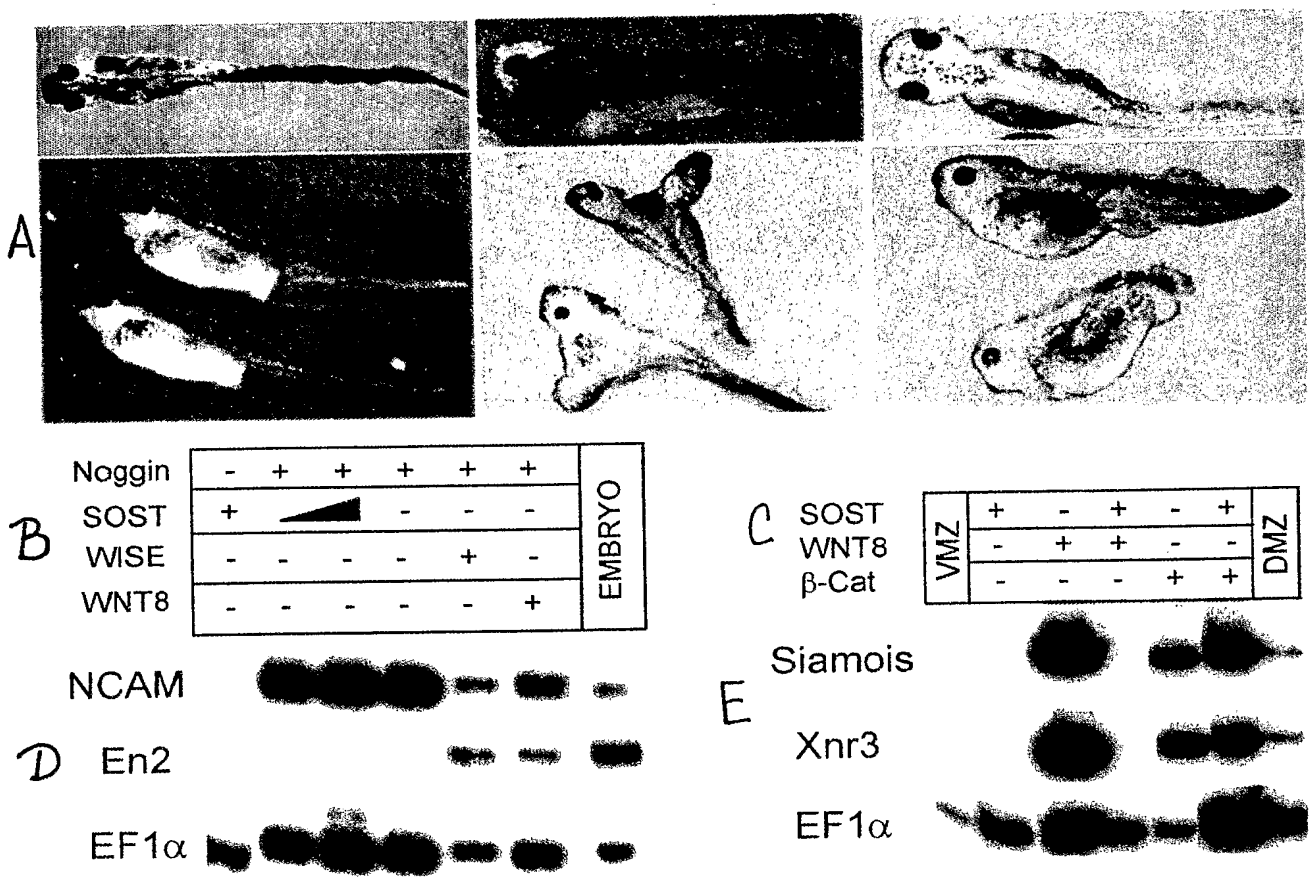

A
B
Noggin
SOST
WISE
WNT8
EMBRYO
C
SOST
WNT8
β-Cat
VMZ
DMZ
D
NCAM
En2
EF1α
E
Siamois
Xnr3
EF1α

Fig. 11

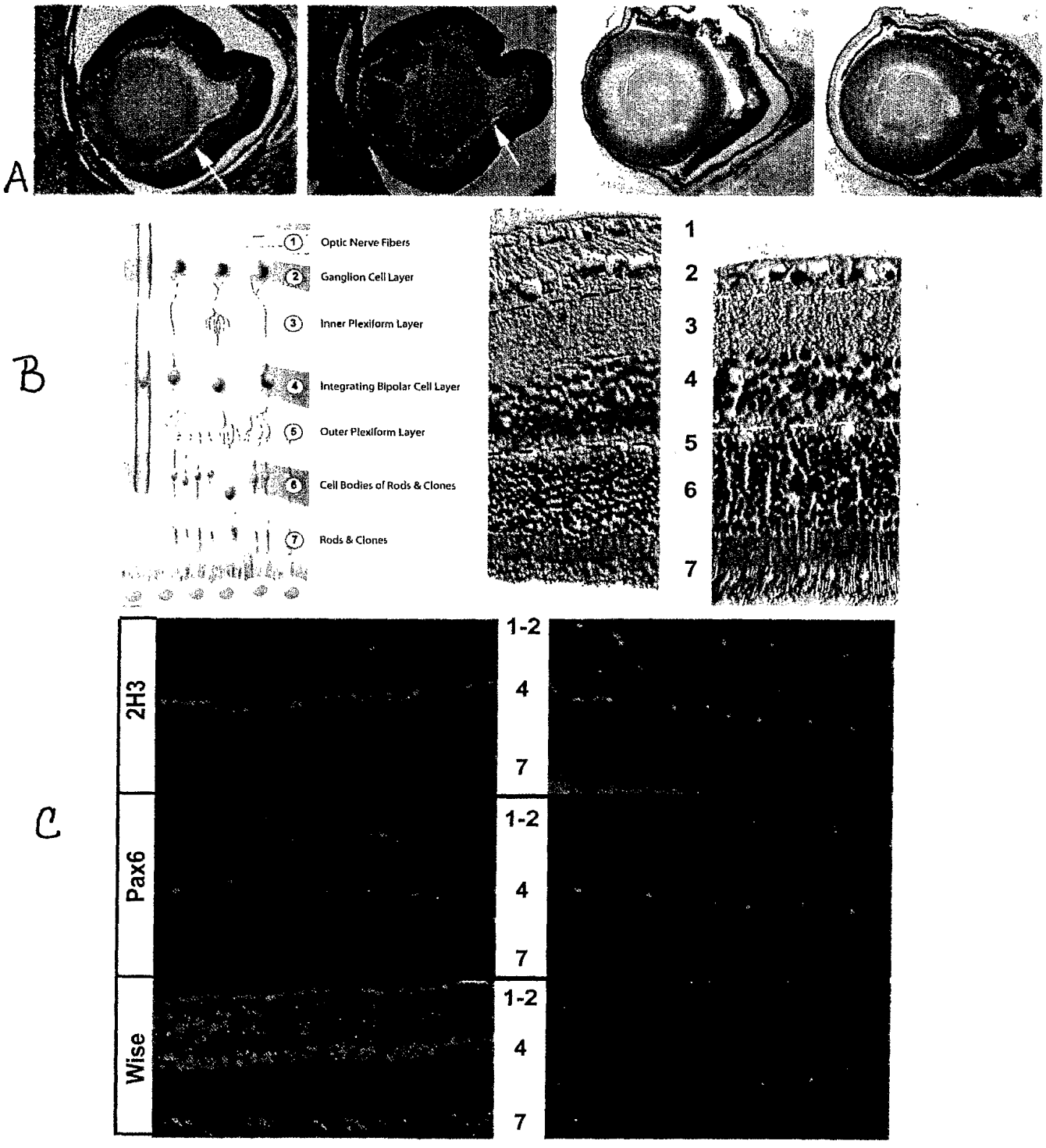

A
B
C
1 Optic Nerve Fibers
2 Ganglion Cell Layer
3 Inner Plexiform Layer
4 Integrating Bipolar Cell Layer
5 Outer Plexiform Layer
6 Cell Bodies of Rods & Clones
7 Rods & Clones
1
2
3
4
5
6
7
2H3
Pax6
Wise
1-2
4
7

Fig. 12

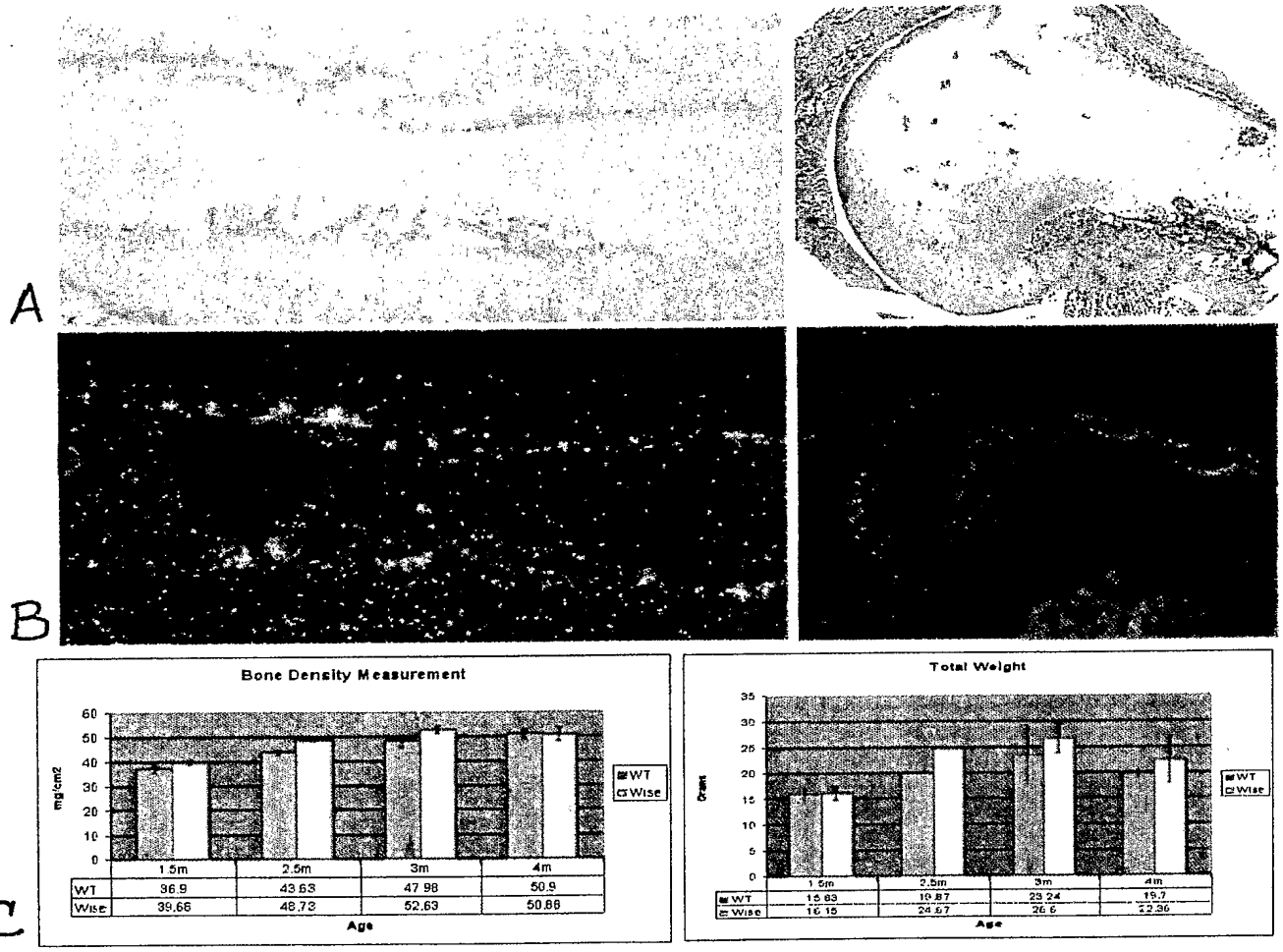

A
B
C
Bone Density Measurement
mg/cm2
60
50
40
30
20
10
0
1.5m
2.5m
3m
4m
WT
Wise
96.9
43.63
47.98
50.9
39.66
48.73
52.63
50.86
Age
WT
Wise
Total Weight
Gram
35
30
25
20
15
10
5
0
1.5m
2.5m
3m
4m
15.63
19.87
23.24
19.7
16.15
24.67
26.6
22.36
Age

Fig. 13

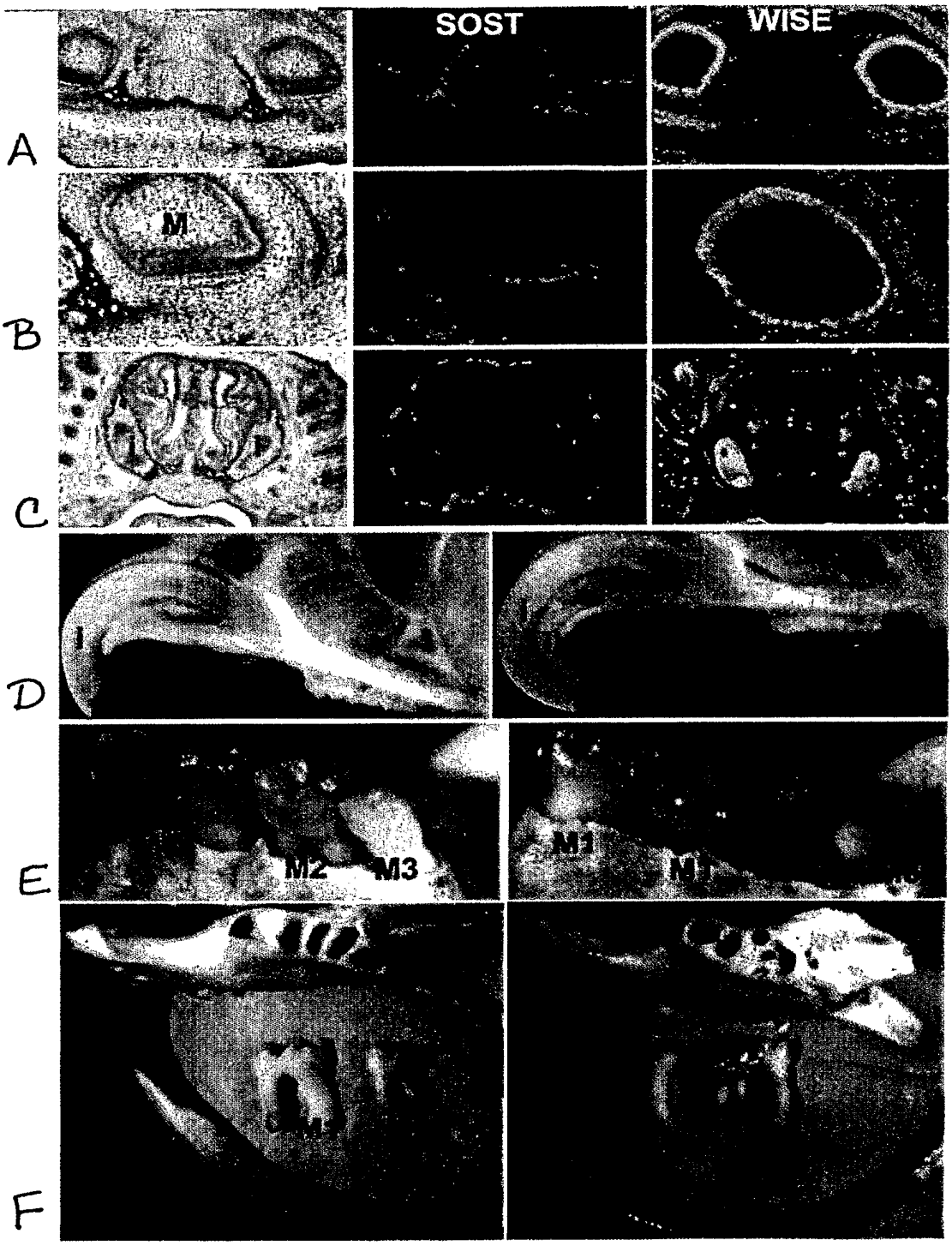


Fig. 14

Nonprovisional IP-017.ST25.txt
SEQUENCE LISTING

<110> Krumlauf, Robb
Ellies, Debra

<120> COMPOSITIONS AND METHODS FOR REGULATING BONE DEPOSITION

<130> 40716-IP-017

<150> 60/388,970
<151> 2002-06-14

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<170> PatentIn version 3.2

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<223> n is a, c, g, or t

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ccggcacacc ccagcagcaa cagcaccctg aatcaagcca ggaatggagg caggcatttc 180

agtagcactg gactggatcg aaacagtcga gttcaagtgg gctgcaggga actgcggtcc 240

accaaataca tttcggacgg ccagtgcacc agcatcagcc ctntgaagga gctggtgtgc 300

gcgggcgagt gcttgccccc gccggtgctt cccaactgga tcggaggagg ctatggaaca 360

aagtactgga gccggaggag ctntcaggag tggcggtgtg tcaacgacaa gacgcgcacc 420

cagaggatcc agctgcagtg tcaggacggc agcacgcgca cctacaaaat caccgtggtc 480

acggcgtgca agtgcaagag gtacacccgt cagcacaacg agtccagcca caactttgaa 540

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agcaagcaca gtctgagc 618

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<211> 3311
<212> DNA
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aattaaccag ctcttcagtc aagcaaatcc tctactcacc atgcttcctc ctgccattca 120

tttctatctc cttccccttg catgcatcct aatgaaaagc tgtttggctt ttaaaaatga 180

tgccacagaa atcctttatt cacatgtggt taaacctgtt ccagcacacc ccagcagcaa 240

cagcacgttg aatcaagcca gaaatggagg caggcatttc agtaacactg gactggatcg 300

gaacagtaag tgtgttttac ttgtacagtt ttttttttc ttttctggta gcattagctc 360

acattcctgt agaattgttt tattggtaac taacctgaac cgtatatatg ttgtgaaaca 420

atttgggagt aatctgctgc atgtgcaggt tggcattctt ccctaggtag tgattttaaa 480

gttaacctaa ctaaaacagt ggtttaatag tgcaagcaca gactgaagtt ttatcaaaca 540

tccacaaaga aaacatttcc aggaattaaa ctattgtttt gtcaaaatca tgcaaaatga 600

ccattttaaa aagtattgtt ttagatagct caagttccgg ttgttttgtc aatttatttc 660

agggcatatg caattttggt aaagtgtata aacgtaacta atatatatta ttagttacca 720

tccacaaata aatataggga atcacaaggg aaaaaaggaa gcttccagga gaaaaaattt 780

gtttacattg gatttctaaa atatgtctag tgagatagtc aaaagttttg atgatgctca 840

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gttgtcccat tcaaaattta gataattgtg tatttctgtg acagactggg gacatttttg 960

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aaatcttttg cctctccttc ttcactccat tcaactacga aaagtagttt tgacttttga 1200

aaagtcaaag caaatttgac tgttaatgtc taagaaagct aggatgtttt aactttcacg 1260

aagctggttg cttttaagta cacaggacat atctgattat tattagatta ctgagcaatg 1320

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<210> 45
<211> 206
<212> PRT
<213> MOUSE

<220>
<221> misc_feature
<222> (95)..(95)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (128)..(128)
<223> Xaa can be any naturally occurring amino acid

<400> 45

Met Leu Pro Pro Ala Ile His Leu Ser Leu Ile Pro Leu Leu Cys Ile
1 5 10 15

Leu Met Arg Asn Cys Leu Ala Phe Lys Asn Asp Ala Thr Glu Ile Leu
20 25 30

Tyr Ser His Val Val Lys Pro Val Pro Ala His Pro Ser Ser Asn Ser
35 40 45

Thr Leu Asn Gln Ala Arg Asn Gly Gly Arg His Phe Ser Ser Thr Gly
50 55 60

Leu Asp Arg Asn Ser Arg Val Gln Val Gly Cys Arg Glu Leu Arg Ser
65 70 75 80

Thr Lys Tyr Ile Ser Asp Gly Gln Cys Thr Ser Ile Ser Pro Xaa Lys
85 90 95

Glu Leu Val Cys Ala Gly Glu Cys Leu Pro Leu Pro Val Leu Pro Asn
100 105 110

Trp Ile Gly Gly Gly Tyr Gly Thr Lys Tyr Trp Ser Arg Arg Ser Xaa
115 120 125

Gln Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln
130 135 140

Leu Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val
145 150 155 160

Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser
165 170 175

His Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His Arg
180 185 190

Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser
195 200 205

<210> 46
<211> 211
<212> PRT
<213> MOUSE

<400> 46

Met Gln Pro Ser Leu Ala Pro Cys Leu Ile Cys Leu Leu Val His Ala
1 5 10 15

Ala Phe Cys Ala Val Glu Gly Gln Gly Trp Gln Ala Phe Arg Asn Asp
20 25 30

Ala Thr Glu Val Ile Pro Gly Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro
50 55 60

His His Pro Tyr Asp Ala Lys Gly Val Ser Glu Tyr Ser Cys Arg Glu
65 70 75 80

Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys Arg Ser Ala Lys
85 90 95

Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu
100 105 110

Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro
115 120 125

Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu
130 135 140

Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val
145 150 155 160

Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu
165 170 175

Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys
180 185 190

Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu Glu
195 200 205

Asn Ala Tyr
210

<210> 47
<211> 211
<212> PRT
<213> MOUSE

<400> 47

Met Gln Pro Ser Leu Ala Pro Cys Leu Ile Cys Leu Leu Val His Ala
1 5 10 15

Ala Phe Cys Ala Val Glu Gly Gln Gly Trp Gln Ala Phe Arg Asn Asp
20 25 30

Ala Thr Glu Val Ile Pro Gly Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro
50 55 60

His His Pro Tyr Asp Ala Lys Asp Val Ser Glu Tyr Ser Cys Arg Glu
65 70 75 80

Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys Arg Ser Ala Lys
85 90 95

Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu
100 105 110

Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro
115 120 125

Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu
130 135 140

Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val
145 150 155 160

Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu
165 170 175

Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys
180 185 190

Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu Glu
195 200 205

Asn Ala Tyr
210

<210> 48
<211> 211
<212> PRT
<213> MOUSE

<400> 48

Met Gln Pro Ser Leu Ala Pro Cys Leu Ile Cys Leu Leu Val His Ala
1 5 10 15

Ala Phe Cys Ala Val Glu Gly Gln Gly Trp Gln Ala Phe Arg Asn Asp
20 25 30

Ala Thr Glu Val Ile Pro Gly Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro
50 55 60

His His Pro Tyr Asp Ala Lys Gly Val Ser Glu Tyr Ser Cys Arg Glu
65 70 75 80

Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys Arg Ser Ala Lys
85 90 95

Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu
100 105 110

Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro
115 120 125

Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu
130 135 140

Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val
145 150 155 160

Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu

165 170 175

Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys
180 185 190

Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu Glu
195 200 205

Asn Ala Tyr
210

<210> 49
<211> 205
<212> PRT
<213> MOUSE

<400> 49

Met Gln Pro Ser Leu Ala Pro Cys Leu Ile Cys Leu Leu Val His Ala
1 5 10 15

Ala Phe Cys Ala Val Glu Gly Gln Gly Trp Gln Ala Phe Arg Asn Asp
20 25 30

Ala Thr Glu Val Ile Pro Gly Leu Gly Glu Tyr Pro Glu Pro Thr Pro
35 40 45

Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro
50 55 60

His His Pro Tyr Asp Ala Lys Asp Val Ser Glu Tyr Ser Cys Arg Glu
65 70 75 80

Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys Arg Ser Ala Lys
85 90 95

Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu
100 105 110

Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro
115 120 125

Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu
130 135 140

Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val
145 150 155 160

Ala Ser Cys Lys Cys Lys Arg Pro Thr Arg Phe His Asn Gln Ser Glu
165 170 175

Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys
180 185 190

Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala
195 200 205

<210> 50
<211> 213
<212> PRT
<213> HOMO SAPIENS

<400> 50

Met Gln Leu Pro Leu Ala Leu Cys Leu Val Cys Leu Leu Val His Thr
1 5 10 15

Ala Phe Arg Val Val Glu Gly Gln Gly Trp Gln Ala Phe Lys Asn Asp
20 25 30

Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
50 55 60

Pro Pro His His Pro Phe Glu Thr Lys Asp Val Ser Glu Tyr Ser Cys
65 70 75 80

Arg Glu Leu His Phe Thr Arg Tyr Val Thr Asp Gly Pro Cys Arg Ser
85 90 95

Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala
100 105 110

Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser
115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
130 135 140

Gln Leu Leu Cys Pro Gly Gly Glu Ala Pro Arg Ala Arg Lys Val Arg
145 150 155 160

Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln
165 170 175

Ser Glu Leu Lys Asp Phe Gly Thr Glu Ala Ala Arg Pro Gln Lys Gly
180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Ser Ala Lys Ala Asn Gln Ala Glu
195 200 205

Leu Glu Asn Ala Tyr
210

<210> 51
<211> 213
<212> PRT
<213> HOMO SAPIENS

<400> 51

Met Gln Leu Pro Leu Ala Leu Cys Leu Val Cys Leu Leu Val His Thr
1 5 10 15

Ala Phe Arg Val Val Glu Gly Gln Gly Trp Gln Ala Phe Lys Asn Asp
20 25 30

Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
50 55 60

Pro Pro His His Pro Phe Glu Thr Lys Gly Val Ser Glu Tyr Ser Cys
65 70 75 80

Arg Glu Leu His Phe Thr Arg Tyr Val Thr Asp Gly Pro Cys Arg Ser
85 90 95

Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala
100 105 110

Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser
115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
130 135 140

Gln Leu Leu Cys Pro Gly Gly Glu Ala Pro Arg Ala Arg Lys Val Arg
145 150 155 160

Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln
165 170 175

Ser Glu Leu Lys Asp Phe Gly Thr Glu Ala Ala Arg Pro Gln Lys Gly
180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Ser Ala Lys Ala Asn Gln Ala Glu
195 200 205

Leu Glu Asn Ala Tyr
210

<210> 52
<211> 206
<212> PRT
<213> CHICK

<400> 52

Met Leu Leu Ser Ala Ile His Phe Tyr Gly Leu Leu Leu Ala Cys Thr
1 5 10 15

Phe Thr Arg Ser Tyr Ser Ala Phe Lys Asn Asp Ala Thr Glu Ile Leu
20 25 30

Tyr Ser His Val Val Lys Pro Ala Pro Ala Ser Pro Ser Ser Asn Ser
35 40 45

Thr Leu Asn Gln Ala Arg Asn Gly Gly Arg His Tyr Ala Gly Thr Gly
50 55 60

Ser Asp Arg Asn Asn Arg Val Gln Val Gly Cys Arg Glu Leu Arg Ser
65 70 75 80

Thr Lys Tyr Ile Ser Asp Gly Gln Cys Thr Ser Ile Asn Pro Leu Lys
85 90 95

Glu Leu Val Cys Ala Gly Glu Cys Leu Pro Leu Pro Leu Leu Pro Asn
100 105 110

Trp Ile Gly Gly Gly Tyr Gly Thr Lys Tyr Trp Ser Arg Arg Ser Ser
115 120 125

Gln Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln
130 135 140

Leu Gln Cys Gln Asp Gly Ser Ile Arg Thr Tyr Lys Ile Thr Val Val
145 150 155 160

Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser
165 170 175

His Asn Phe Glu Gly Thr Ser Gln Ala Lys Pro Val Gln His His Lys
180 185 190

Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Thr Ser
195 200 205

<210> 53
<211> 213
<212> PRT
<213> RAT

<400> 53

Met Gln Leu Ser Leu Ala Pro Cys Leu Ala Cys Leu Leu Val His Ala
1 5 10 15

Ala Phe Val Ala Val Glu Ser Gln Gly Trp Gln Ala Phe Lys Asn Asp
20 25 30

Ala Thr Glu Ile Ile Pro Gly Leu Arg Glu Tyr Pro Glu Pro Pro Gln
35 40 45

Glu Leu Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
50 55 60

Pro Pro His His Pro Tyr Asp Thr Lys Asp Val Ser Glu Tyr Ser Cys
65 70 75 80

Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro Cys Arg Ser
85 90 95

Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala
100 105 110

Arg Leu Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn
115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
130 135 140

Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg
145 150 155 160

Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln
165 170 175

Ser Glu Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly
180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu
195 200 205

Leu Glu Asn Ala Tyr
210

<210> 54
<211> 348
<212> PRT
<213> *MOUSE*

<400> 54

Met Leu Ala Ser Val Ala Gly Pro Ile Ser Leu Ala Leu Val Leu Leu
1 5 10 15

Ala Leu Cys Thr Arg Pro Ala Thr Gly Gln Asp Cys Ser Ala Gln Cys
20 25 30

Gln Cys Ala Ala Glu Ala Ala Pro His Cys Pro Ala Gly Val Ser Leu
35 40 45

Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu Gly
50 55 60

Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu Phe
65 70 75 80

Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr Ala
85 90 95

Lys Asp Gly Ala Pro Cys Val Phe Gly Gly Ser Val Tyr Arg Ser Gly
100 105 110

Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp Gly
115 120 125

Ala Val Gly Cys Val Pro Leu Cys Ser Met Asp Val Arg Leu Pro Ser
130 135 140

Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys Cys
145 150 155 160

Lys Glu Trp Val Cys Asp Glu Pro Lys Asp Arg Thr Ala Val Gly Pro
165 170 175

Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro Thr
180 185 190

Met Met Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala Cys
195 200 205

Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp Asn
210 215 220

Thr Phe Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg Pro
225 230 235 240

Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys Ile
245 250 255

Arg Thr Pro Lys Ile Ala Lys Pro Val Lys Phe Glu Leu Ser Gly Cys
260 265 270

Thr Ser Val Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr Asp
275 280 285

Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu Phe
290 295 300

Lys Cys Pro Asp Gly Glu Ile Met Lys Lys Asn Met Met Phe Ile Lys
305 310 315 320

Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe Glu
325 330 335

Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala
340 345

<210> 55
<211> 349
<212> PRT
<213> HOMO SAPIENS

<400> 55

Met Thr Ala Ala Ser Met Gly Pro Val Arg Val Ala Phe Val Val Leu
1 5 10 15

Leu Ala Leu Cys Ser Arg Pro Ala Val Gly Gln Asn Cys Ser Gly Pro
20 25 30

Cys Arg Cys Pro Asp Glu Pro Ala Pro Arg Cys Pro Ala Gly Val Ser
35 40 45

Leu Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu
50 55 60

Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
65 70 75 80

Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr
85 90 95

Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly Thr Val Tyr Arg Ser
100 105 110

Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp
115 120 125

Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu Pro
130 135 140

Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys
145 150 155 160

Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln Thr Val Val Gly
165 170 175

Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro
180 185 190

Thr Met Ile Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala
195 200 205

Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
210 215 220

Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
225 230 235 240

Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
245 250 255

Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
260 265 270

Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr
275 280 285

Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu
290 295 300

Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile
305 310 315 320

Lys Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe
325 330 335

Glu Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala
340 345

<210> 56
<211> 347
<212> PRT
<213> RAT

<400> 56

Met Leu Ala Ser Val Ala Gly Pro Val Ser Leu Ala Leu Val Leu Leu
1 5 10 15

Leu Cys Thr Arg Pro Ala Thr Gly Gln Asp Cys Ser Ala Gln Cys Gln
20 25 30

Cys Ala Ala Glu Ala Ala Pro Arg Cys Pro Ala Gly Val Ser Leu Val
35 40 45

Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu Gly Glu
50 55 60

Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu Phe Cys
65 70 75 80

Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr Ala Lys
85 90 95

Asp Gly Ala Pro Cys Val Phe Gly Gly Ser Val Tyr Arg Ser Gly Glu

100 105 110

Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp Gly Ala
115 120 125

Val Gly Cys Val Pro Leu Cys Ser Met Asp Val Arg Leu Pro Ser Pro
130 135 140

Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys Cys Glu
145 150 155 160

Glu Trp Val Cys Asp Glu Pro Lys Asp Arg Thr Val Val Gly Pro Ala
165 170 175

Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro Thr Met
180 185 190

Met Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala Cys Ser
195 200 205

Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Thr
210 215 220

Phe Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg Pro Cys
225 230 235 240

Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys Ile Arg
245 250 255

Thr Pro Lys Ile Ala Lys Pro Val Lys Phe Glu Leu Ser Gly Cys Thr
260 265 270

Ser Val Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr Asp Gly
275 280 285

Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu Phe Lys
290 295 300

Cys Pro Asp Gly Glu Ile Met Lys Lys Asn Met Met Phe Ile Lys Thr
305 310 315 320

Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe Glu Ser
325 330 335

Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala
340 345

<210> 57
<211> 349
<212> PRT
<213> BOVINE

<400> 57

Met Ser Ala Thr Gly Leu Gly Pro Val Arg Cys Ala Phe Val Leu Leu
1 5 10 15

Leu Ala Leu Cys Ser Arg Pro Ala Ser Ser Gln Asp Cys Cys Ser Ala
20 25 30

Pro Cys Gln Cys Pro Ala Gly Pro Ala Pro Arg Cys Pro Ala Gly Val
35 40 45

Ser Leu Val Leu Asp Gly Cys Gly Cys Cys Val Cys Ala Lys Gln Leu
50 55 60

Ser Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
65 70 75 80

Phe Cys Asp Phe Gly Ser Pro Thr Asn Arg Lys Ile Gly Val Cys Thr
85 90 95

Ala Lys Asp Gly Ala Pro Tyr Ile Phe Gly Gly Thr Val Tyr Gln Ser
100 105 110

Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp
115 120 125

Gly Ser Val Gly Cys Val Pro Leu Cys Ser Val Asp Val Arg Leu Pro
130 135 140

Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys
145 150 155 160

Cys Glu Glu Trp Val Ser Arg Asp Glu Lys Glu His Thr Val Val Gly
165 170 175

Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro
180 185 190

Thr Met Ile Arg Ala Asn Cys Gln Val Gln Thr Thr Glu Trp Ser Ala
195 200 205

Tyr Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
210 215 220

Asn Ala Phe Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
225 230 235 240

Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
245 250 255

Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Gln Leu Ser Gly
260 265 270

Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Phe Gly Val Cys Thr
275 280 285

Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu
290 295 300

Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Ser Met Met Phe Ile
305 310 315 320

Lys Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe
325 330 335

Glu Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala
340 345

<210> 58
<211> 354
<212> PRT
<213> MOUSE

<400> 58

Met Ser Leu Phe Leu Arg Lys Arg Cys Leu Cys Leu Gly Phe Leu Leu
1 5 10 15

Phe His Leu Leu Ser Gln Val Ser Ala Ser Leu Arg Cys Pro Ser Arg
20 25 30

Cys Pro Pro Lys Cys Pro Ser Ile Ser Pro Thr Cys Ala Pro Gly Val
35 40 45

Arg Ser Val Leu Asp Gly Cys Ser Cys Cys Pro Val Cys Ala Arg Gln
50 55 60

Arg Gly Glu Ser Cys Ser Glu Met Arg Pro Cys Asp Gln Ser Ser Gly
65 70 75 80

Leu Tyr Cys Asp Arg Ser Ala Asp Pro Asn Asn Gln Thr Gly Ile Cys
85 90 95

Met Val Pro Glu Gly Asp Asn Cys Val Phe Asp Gly Val Ile Tyr Arg
100 105 110

Asn Gly Glu Lys Phe Glu Pro Asn Cys Gln Tyr Phe Cys Thr Cys Arg
115 120 125

Asp Gly Gln Ile Gly Cys Leu Pro Arg Cys Gln Leu Asp Val Leu Leu
130 135 140

Pro Gly Pro Asp Cys Pro Ala Pro Arg Lys Val Ala Val Pro Gly Glu
145 150 155 160

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Cys Cys Glu Lys Trp Thr Cys Gly Ser Asp Glu Gln Gly Thr Gln Gly
                165                 170                 175

Thr Leu Gly Gly Leu Ala Leu Pro Ala Tyr Arg Pro Glu Ala Thr Val
            180                 185                 190

Gly Val Glu Val Ser Asp Ser Ser Ile Asn Cys Ile Glu Gln Thr Thr
        195                 200                 205

Glu Trp Ser Ala Cys Ser Lys Ser Cys Gly Met Gly Val Ser Thr Arg
    210                 215                 220

Val Thr Asn Arg Asn Arg Gln Cys Glu Met Val Lys Gln Thr Arg Leu
225                 230                 235                 240

Cys Ile Val Arg Pro Cys Glu Gln Glu Pro Glu Glu Val Thr Asp Lys
                245                 250                 255

Lys Gly Lys Lys Cys Leu Arg Thr Lys Lys Ser Leu Lys Ala Ile His
            260                 265                 270

Leu Gln Phe Glu Asn Cys Thr Ser Leu Tyr Thr Tyr Lys Pro Arg Phe
        275                 280                 285

Cys Gly Val Cys Ser Asp Gly Arg Cys Cys Thr Pro His Asn Thr Lys
    290                 295                 300

Thr Ile Gln Val Glu Phe Gln Cys Leu Pro Gly Glu Ile Ile Lys Lys
305                 310                 315                 320

Pro Val Met Val Ile Gly Thr Cys Thr Cys Tyr Ser Asn Cys Pro Gln
                325                 330                 335

Asn Asn Glu Ala Phe Leu Gln Asp Leu Glu Leu Lys Thr Ser Arg Gly
            340                 345                 350

Glu Ile
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<210> 59
<211> 357
<212> PRT
<213> HOMO SAPIENS

<400> 59

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Met Gln Ser Val Gln Ser Thr Ser Phe Cys Leu Arg Lys Gln Cys Leu
1               5                   10                  15

Cys Leu Thr Phe Leu Leu Leu His Leu Leu Gly Gln Val Ala Ala Thr
            20                  25                  30
```

Gln Arg Cys Pro Pro Gln Cys Pro Gly Arg Cys Pro Ala Thr Pro Pro
35 40 45

Thr Cys Ala Pro Gly Val Arg Ala Val Leu Asp Gly Cys Ser Cys Cys
50 55 60

Leu Val Cys Ala Arg Gln Arg Gly Glu Ser Cys Ser Asp Leu Glu Pro
65 70 75 80

Cys Asp Glu Ser Ser Gly Leu Tyr Cys Asp Arg Ser Ala Asp Pro Ser
85 90 95

Asn Gln Thr Gly Ile Cys Thr Ala Val Glu Gly Asp Asn Cys Val Phe
100 105 110

Asp Gly Val Ile Tyr Arg Ser Gly Glu Lys Phe Gln Pro Ser Cys Lys
115 120 125

Phe Gln Cys Thr Cys Arg Asp Gly Gln Ile Gly Cys Val Pro Arg Cys
130 135 140

Gln Leu Asp Val Leu Leu Pro Glu Pro Asn Cys Pro Ala Pro Arg Lys
145 150 155 160

Val Glu Val Pro Gly Glu Cys Cys Glu Lys Trp Ile Cys Gly Pro Asp
165 170 175

Glu Glu Asp Ser Leu Gly Gly Leu Thr Leu Ala Ala Tyr Arg Pro Glu
180 185 190

Ala Thr Leu Gly Val Glu Val Ser Asp Ser Ser Val Asn Cys Ile Glu
195 200 205

Gln Thr Thr Glu Trp Thr Ala Cys Ser Lys Ser Cys Gly Met Gly Phe
210 215 220

Ser Thr Arg Val Thr Asn Arg Asn Arg Gln Cys Glu Met Leu Lys Gln
225 230 235 240

Thr Arg Leu Cys Met Val Arg Pro Cys Glu Gln Glu Pro Glu Gln Pro
245 250 255

Thr Asp Lys Lys Gly Lys Lys Cys Leu Arg Thr Lys Lys Ser Leu Lys
260 265 270

Ala Ile His Leu Gln Phe Lys Asn Cys Thr Ser Leu His Thr Tyr Lys
275 280 285

Pro Arg Phe Cys Gly Val Cys Ser Asp Gly Arg Cys Cys Thr Pro His
290 295 300

Asn Thr Lys Thr Ile Gln Ala Glu Phe Gln Cys Ser Pro Gly Gln Ile
305 310 315 320

Val Lys Lys Pro Val Met Val Ile Gly Thr Cys Thr Cys His Thr Asn
325 330 335

Cys Pro Lys Asn Asn Glu Ala Phe Leu Gln Glu Leu Glu Leu Lys Thr
340 345 350

Thr Arg Gly Lys Met
355

<210> 60
<211> 379
<212> PRT
<213> MOUSE

<400> 60

Met Ser Ser Ser Thr Phe Arg Thr Leu Ala Val Ala Val Thr Leu Leu
1 5 10 15

His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys His Cys
20 25 30

Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val Gly Leu Val Arg Asp
35 40 45

Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys
50 55 60

Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe
65 70 75 80

Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu
85 90 95

Gly Arg Pro Cys Glu Tyr Asn Ser Arg Ile Tyr Gln Asn Gly Glu Ser
100 105 110

Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val
115 120 125

Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly
130 135 140

Cys Pro Asn Pro Arg Leu Val Lys Val Ser Gly Gln Cys Cys Glu Glu
145 150 155 160

Trp Val Cys Asp Glu Asp Ser Ile Lys Asp Ser Leu Asp Asp Gln Asp
165 170 175

Asp Leu Leu Gly Leu Asp Ala Ser Glu Val Glu Leu Thr Arg Asn Asn

180 185 190

Glu Leu Ile Ala Ile Gly Lys Gly Ser Ser Leu Lys Arg Leu Pro Val
195 200 205

Phe Gly Thr Glu Pro Arg Val Leu Phe Asn Pro Leu His Ala His Gly
210 215 220

Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser Lys Ser
225 230 235 240

Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Pro Glu Cys
245 250 255

Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys Gly Gln
260 265 270

Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys Thr Lys
275 280 285

Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Ser Ser Val
290 295 300

Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys
305 310 315 320

Cys Thr Pro Leu Gln Thr Arg Thr Val Lys Met Arg Phe Arg Cys Glu
325 330 335

Asp Gly Glu Met Phe Ser Lys Asn Val Met Met Ile Gln Ser Cys Lys
340 345 350

Cys Asn Tyr Asn Cys Pro His Pro Asn Glu Ala Ser Phe Arg Leu Tyr
355 360 365

Ser Leu Phe Asn Asp Ile His Lys Phe Arg Asp
370 375

<210> 61
<211> 381
<212> PRT
<213> HOMO SAPIENS

<400> 61

Met Ser Ser Arg Ile Ala Arg Ala Leu Ala Leu Val Val Thr Leu Leu
1 5 10 15

His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys His Cys
20 25 30

Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val Gly Leu Val Arg Asp
35 40 45

Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys
50 55 60

Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe
65 70 75 80

Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu
85 90 95

Gly Arg Pro Cys Glu Tyr Asn Ser Arg Ile Tyr Gln Asn Gly Glu Ser
100 105 110

Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val
115 120 125

Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly
130 135 140

Cys Pro Asn Pro Arg Leu Val Lys Val Thr Gly Gln Cys Cys Glu Glu
145 150 155 160

Trp Val Cys Asp Glu Asp Ser Ile Lys Asp Pro Met Glu Asp Gln Asp
165 170 175

Gly Leu Leu Gly Lys Glu Leu Gly Phe Asp Ala Ser Glu Val Glu Leu
180 185 190

Thr Arg Asn Asn Glu Leu Ile Ala Val Gly Lys Gly Ser Ser Leu Lys
195 200 205

Arg Leu Pro Val Phe Gly Met Glu Pro Arg Ile Leu Tyr Asn Pro Leu
210 215 220

Gln Gly Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser
225 230 235 240

Lys Thr Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Pro
245 250 255

Glu Cys Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys
260 265 270

Gly Gln Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys
275 280 285

Thr Lys Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Leu
290 295 300

Ser Val Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly
305 310 315 320

Arg Cys Cys Thr Pro Gln Leu Thr Arg Thr Val Lys Met Arg Phe Arg
325 330 335

Cys Glu Asp Gly Glu Thr Phe Ser Lys Asn Val Met Met Ile Gln Ser
340 345 350

Cys Lys Cys Asn Tyr Asn Cys Pro His Ala Asn Glu Ala Ala Phe Pro
355 360 365

Phe Tyr Arg Leu Phe Asn Asp Ile His Lys Phe Arg Asp
370 375 380

<210> 62
<211> 379
<212> PRT
<213> RAT

<400> 62

Met Ser Ser Ser Thr Ile Lys Thr Leu Ala Val Ala Val Thr Leu Leu
1 5 10 15

His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ser Cys His Cys
20 25 30

Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val Gly Leu Val Arg Asp
35 40 45

Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys
50 55 60

Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe
65 70 75 80

Gly Ala Asn Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu
85 90 95

Gly Arg Pro Cys Glu Tyr Asn Ser Arg Ile Tyr Gln Asn Gly Glu Ser
100 105 110

Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val
115 120 125

Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly
130 135 140

Cys Pro Asn Pro Arg Leu Val Lys Val Ser Gly Gln Cys Cys Glu Glu
145 150 155 160

Trp Val Cys Asp Glu Asp Ser Ile Lys Asp Ser Leu Asp Asp Gln Asp
165 170 175

Asp Leu Leu Gly Phe Asp Ala Ser Glu Val Glu Leu Thr Arg Asn Asn
180 185 190

Glu Leu Ile Ala Thr Gly Lys Gly Ser Ser Leu Lys Arg Leu Pro Val
195 200 205

Phe Gly Thr Glu Pro Arg Val Leu Tyr Asn Pro Leu His Ala His Gly
210 215 220

Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser Lys Ser
225 230 235 240

Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Pro Glu Cys
245 250 255

Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys Gly Gln
260 265 270

Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys Thr Lys
275 280 285

Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Ser Ser Val
290 295 300

Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys
305 310 315 320

Cys Thr Pro Leu Gln Thr Arg Thr Val Lys Met Arg Phe Arg Cys Glu
325 330 335

Asp Gly Glu Met Phe Ser Lys Asn Val Met Met Ile Gln Ser Cys Lys
340 345 350

Cys Asn Tyr Asn Cys Pro His Pro Asn Glu Ala Ser Phe Arg Leu Tyr
355 360 365

Ser Leu Phe Asn Asp Ile His Lys Phe Arg Asp
370 375

<210> 63
<211> 375
<212> PRT
<213> XENOPUS

<400> 63

Met Ser Phe Leu Ala Leu Asn Pro Val Leu Ala Ile Ala Leu Leu Ser
1 5 10 15

Gly Phe Ile Asp Leu Ala Val Ser Ser Cys Pro Ala Val Cys Gln Cys
20 25 30

Pro Val Glu Val Pro Lys Cys Ala Pro Gly Val Gly Leu Val Leu Asp
35 40 45

Gly Cys Gly Cys Cys Lys Ile Cys Ala Lys Gln Leu Asn Glu Asp Cys
50 55 60

Ser Lys Thr His Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe
65 70 75 80

Gly Ala Ser Ser Arg Ala Ile Lys Gly Ile Cys Arg Ala Lys Ser Glu
85 90 95

Gly Arg Pro Cys Glu Tyr Asn Ser Lys Ile Tyr Gln Asn Gly Glu Ser
100 105 110

Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val
115 120 125

Gly Cys Leu Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly
130 135 140

Cys Pro Asn Pro Arg Leu Val Lys Val Pro Gly Gln Cys Cys Glu Glu
145 150 155 160

Trp Val Cys Asp Glu Ala Lys Asp Pro Val Asp Glu Met Asp Asp Phe
165 170 175

Phe Asn Lys Glu Phe Gly Met Asp Thr Asn Glu Gly Glu Leu Thr Arg
180 185 190

Lys Asn Glu Phe Val Ala Val Ile Lys Gly Gly Leu Lys Met Leu Pro
195 200 205

Val Phe Gly Ser Asp Pro Gln Ser His Val Val Glu Asn Ser Lys Cys
210 215 220

Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser Lys Thr Cys Gly Thr
225 230 235 240

Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Ser Asn Cys Arg Leu Val
245 250 255

Arg Glu Thr Arg Ile Cys Glu Val Arg Pro Cys Gly Gln Pro Ser Tyr
260 265 270

Thr Ser Leu Lys Lys Gly Lys Lys Cys Thr Lys Thr Lys Lys Ser Gln
275 280 285

Ala Pro Val Arg Tyr Thr Tyr Ala Gly Cys Ser Ser Val Lys Lys Tyr
290 295 300

Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys Cys Thr Pro
305 310 315 320

Gln Gln Thr Arg Thr Val Lys Ile Arg Phe Arg Cys Glu Asp Gly Glu
325 330 335

Thr Phe Thr Lys Asn Val Met Met Ile Gln Ser Cys Arg Cys Asn Tyr
340 345 350

Asn Cys Pro His Thr Asn Glu Ala Tyr Pro Tyr Tyr Arg Leu Phe Asn
355 360 365

Asp Ile His Lys Phe Arg Asp
370 375

<210> 64
<211> 184
<212> PRT
<213> MOUSE

<400> 64

Met Asn Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Leu Gly
1 5 10 15

Thr Leu Leu Pro Thr Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala
20 25 30

Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
35 40 45

Ser Pro Pro Gln Pro Gly Ser Arg Thr Arg Gly Arg Gly Gln Gly Arg
50 55 60

Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala
65 70 75 80

Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr
85 90 95

Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr
100 105 110

Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro
115 120 125

Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys
130 135 140

Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu
145 150 155 160

Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys

165 170 175

Arg Cys Ile Ser Ile Asp Leu Asp
180

<210> 65
<211> 184
<212> PRT
<213> MOUSE

<400> 65

Met Asn Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Leu Gly
1 5 10 15

Thr Leu Leu Pro Thr Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala
20 25 30

Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
35 40 45

Ser Pro Pro Gln Pro Gly Ser Arg Thr Arg Gly Arg Gly Gln Gly Arg
50 55 60

Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala
65 70 75 80

Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr
85 90 95

Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr
100 105 110

Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro
115 120 125

Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys
130 135 140

Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu
145 150 155 160

Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys
165 170 175

Arg Cys Ile Ser Ile Asp Leu Asp
180

<210> 66
<211> 184
<212> PRT
<213> HOMO SAPIENS

<400> 66

Met Ser Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Leu Gly
1 5 10 15

Thr Leu Leu Pro Ala Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala
20 25 30

Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
35 40 45

Ser Pro Gln Gln Pro Gly Ser Arg Asn Arg Gly Arg Gly Gln Gly Arg
50 55 60

Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala
65 70 75 80

Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr
85 90 95

Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr
100 105 110

Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro
115 120 125

Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys
130 135 140

Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu
145 150 155 160

Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys
165 170 175

Arg Cys Ile Ser Ile Asp Leu Asp
180

<210> 67
<211> 4545
<212> PRT
<213> MOUSE

<400> 67

Met Leu Thr Pro Pro Leu Leu Leu Leu Leu Pro Leu Leu Ser Ala Leu
1 5 10 15

Val Ser Gly Ala Thr Met Asp Ala Pro Lys Thr Cys Ser Pro Lys Gln
20 25 30

Phe Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys
35 40 45

Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu Ala Pro Glu Ile
50 55 60

Cys Pro Gln Ser Lys Ala Gln Arg Cys Pro Pro Asn Glu His Ser Cys
65 70 75 80

Leu Gly Thr Glu Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Ile
85 90 95

Gln Asp Cys Met Asp Gly Ser Asp Glu Gly Ala His Cys Arg Glu Leu
100 105 110

Arg Ala Asn Cys Ser Arg Met Gly Cys Gln His His Cys Val Pro Thr
115 120 125

Pro Ser Gly Pro Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Gln Ala
130 135 140

Asp Gly Lys Thr Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr
145 150 155 160

Cys Ser Gln Leu Cys Thr Asn Thr Asp Gly Ser Phe Thr Cys Gly Cys
165 170 175

Val Glu Gly Tyr Leu Leu Gln Pro Asp Asn Arg Ser Cys Lys Ala Lys
180 185 190

Asn Glu Pro Val Asp Arg Pro Pro Val Leu Leu Ile Ala Asn Ser Gln
195 200 205

Asn Ile Leu Ala Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr
210 215 220

Pro Thr Ser Thr Arg Gln Thr Thr Ala Met Asp Phe Ser Tyr Ala Asn
225 230 235 240

Glu Thr Val Cys Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln
245 250 255

Leu Lys Cys Ala Arg Met Pro Gly Leu Lys Gly Phe Val Asp Glu His
260 265 270

Thr Ile Asn Ile Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile
275 280 285

Asp Trp Leu Thr Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg
290 295 300

Ile Phe Val Cys Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp
305 310 315 320

Leu Glu Leu Tyr Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly
325 330 335

Lys Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys
340 345 350

Asp Met Asp Gly Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val
355 360 365

Phe Pro His Gly Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp
370 375 380

Ala Asp Ala Tyr Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys
385 390 395 400

Gly Arg Gln Thr Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly
405 410 415

Leu Thr Val Phe Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala
420 425 430

Asn Thr Gln Gln Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser
435 440 445

Thr Glu Tyr Gln Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His
450 455 460

Ile Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu
465 470 475 480

Asn Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu
485 490 495

Ala Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser
500 505 510

Leu Gly Ser Asp Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe
515 520 525

Leu Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met
530 535 540

Gly Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met
545 550 555 560

Asn Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe
565 570 575

Ala Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr
580 585 590

Glu Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val
595 600 605

Ala Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro
610 615 620

Lys Lys Thr Ile Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg
625 630 635 640

Lys Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val
645 650 655

Asp Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro
660 665 670

Lys Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser
675 680 685

His Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly
690 695 700

Leu Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe
705 710 715 720

Tyr Asp Arg Ile Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile
725 730 735

Val Tyr Glu Gly Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His
740 745 750

Gly Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg
755 760 765

Leu Glu Arg Gly Val Ala Gly Ala Pro Pro Thr Val Thr Leu Leu Arg
770 775 780

Ser Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln
785 790 795 800

Gln Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser
805 810 815

Ser Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu
820 825 830

Asp Gln Val Leu Asp Thr Asp Gly Val Thr Cys Leu Ala Asn Pro Ser
835 840 845

Tyr Val Pro Pro Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn
850 855 860

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Asn Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys
865                 870                 875                 880

Leu Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys
                885                 890                 895

Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg
            900                 905                 910

Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser
        915                 920                 925

Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys
    930                 935                 940

Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp
945                 950                 955                 960

Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr
                965                 970                 975

Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn
            980                 985                 990

Ile Asn Trp Arg Cys Asp Asn Asp  Asn Asp Cys Gly Asp  Asn Ser Asp
        995                 1000                1005

Glu Ala  Gly Cys Ser His Ser  Cys Ser Ser Thr Gln  Phe Lys Cys
    1010                1015                1020

Asn Ser  Gly Arg Cys Ile Pro  Glu His Trp Thr Cys  Asp Gly Asp
    1025                1030                1035

Asn Asp  Cys Gly Asp Tyr Ser  Asp Glu Thr His Ala  Asn Cys Thr
    1040                1045                1050

Asn Gln  Ala Thr Arg Pro Pro  Gly Gly Cys His Ser  Asp Glu Phe
    1055                1060                1065

Gln Cys  Arg Leu Asp Gly Leu  Cys Ile Pro Leu Arg  Trp Arg Cys
    1070                1075                1080

Asp Gly  Asp Thr Asp Cys Met  Asp Ser Ser Asp Glu  Lys Ser Cys
    1085                1090                1095

Glu Gly  Val Thr His Val Cys  Asp Pro Asn Val Lys  Phe Gly Cys
    1100                1105                1110

Lys Asp  Ser Ala Arg Cys Ile  Ser Lys Ala Trp Val  Cys Asp Gly
    1115                1120                1125
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Leu Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser
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Val Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Lys Asp Asp Cys
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Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp Gln Cys Ser Leu
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Asn Asn Gly Gly Cys Ser His Asn Cys Ser Val Ala Pro Gly Glu
1190 1195 1200

Gly Ile Val Cys Ser Cys Pro Leu Gly Met Glu Leu Gly Ser Asp
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Asn His Thr Cys Gln Ile Gln Ser Tyr Cys Ala Lys His Leu Lys
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Cys Ser Gln Lys Cys Asp Gln Asn Lys Phe Ser Val Lys Cys Ser
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Cys Tyr Glu Gly Trp Val Leu Glu Pro Asp Gly Glu Ser Cys Arg
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Ser Leu Asp Pro Phe Lys Pro Phe Ile Ile Phe Ser Asn Arg His
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Glu Ile Arg Arg Ile Asp Leu His Lys Gly Asp Tyr Ser Val Leu
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Val Pro Gly Leu Arg Asn Thr Ile Ala Leu Asp Phe His Leu Ser
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Gln Ser Ala Leu Tyr Trp Thr Asp Val Val Glu Asp Lys Ile Tyr
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Arg Gly Lys Leu Leu Asp Asn Gly Ala Leu Thr Ser Phe Glu Val
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Val Ile Gln Tyr Gly Leu Ala Thr Pro Glu Gly Leu Ala Val Asp
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Trp Ile Ala Gly Asn Ile Tyr Trp Val Glu Ser Asn Leu Asp Gln
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Ile Glu Val Ala Lys Leu Asp Gly Thr Leu Arg Thr Thr Leu Leu
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Ala Gly Asp Ile Glu His Pro Arg Ala Ile Ala Leu Asp Pro Arg
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Asp Gly Ile Leu Phe Trp Thr Asp Trp Asp Ala Ser Leu Pro Arg
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Arg Glu Thr Gly Ser Gly Gly Trp Pro Asn Gly Leu Thr Val Asp
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Tyr Leu Glu Lys Arg Ile Leu Trp Ile Asp Ala Arg Ser Asp Ala
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Cys Tyr Glu Phe Lys Lys Phe Leu Leu Tyr Ala Arg Gln Met Glu
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Ile Arg Gly Val Asp Leu Asp Ala Pro Tyr Tyr Asn Tyr Ile Ile
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Ser Phe Thr Val Pro Asp Ile Asp Asn Val Thr Val Leu Asp Tyr
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Asp Ala Arg Glu Gln Arg Val Tyr Trp Ser Asp Val Arg Thr Gln
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Ala Ile Lys Arg Ala Phe Ile Asn Gly Thr Gly Val Glu Thr Val
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Val Ser Ala Asp Leu Pro Asn Ala His Gly Leu Ala Val Asp Trp
1655 1660 1665

Val Ser Arg Asn Leu Phe Trp Thr Ser Tyr Asp Thr Asn Lys Lys
1670 1675 1680

Gln Ile Asn Val Ala Arg Leu Asp Gly Ser Phe Lys Asn Ala Val
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Val Gln Gly Leu Glu Gln Pro His Gly Leu Val Val His Pro Leu
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Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asp Asn Ile Ser Met Ala
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Asn Met Asp Gly Ser Asn His Thr Leu Leu Phe Ser Gly Gln Lys
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Gly Pro Val Gly Leu Ala Ile Asp Phe Pro Glu Ser Lys Leu Tyr
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Trp Ile Ser Ser Gly Asn His Thr Ile Asn Arg Cys Asn Leu Asp
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Gly Ser Glu Leu Glu Val Ile Asp Thr Met Arg Ser Gln Leu Gly
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Lys Ala Thr Ala Leu Ala Ile Met Gly Asp Lys Leu Trp Trp Ala
1790 1795 1800

Asp Gln Val Ser Glu Lys Met Gly Thr Cys Asn Lys Ala Asp Gly
1805 1810 1815

Ser Gly Ser Val Val Leu Arg Asn Ser Thr Thr Leu Val Met His
1820 1825 1830

Met Lys Val Tyr Asp Glu Ser Ile Gln Leu Glu His Glu Gly Thr
1835 1840 1845

Asn Pro Cys Ser Val Asn Asn Gly Asp Cys Ser Gln Leu Cys Leu
1850 1855 1860

Pro Thr Ser Glu Thr Thr Arg Ser Cys Met Cys Thr Ala Gly Tyr
1865 1870 1875

Ser Leu Arg Ser Gly Gln Gln Ala Cys Glu Gly Val Gly Ser Phe
1880 1885 1890

Leu Leu Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro Leu Asp
1895 1900 1905

Pro Asn Asp Lys Ser Asp Ala Leu Val Pro Val Ser Gly Thr Ser
1910 1915 1920

Leu Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr Ile Tyr
1925 1930 1935

Trp Val Asp Met Gly Leu Ser Thr Ile Ser Arg Ala Lys Arg Asp
1940 1945 1950

Gln Thr Trp Arg Glu Asp Val Val Thr Asn Gly Ile Gly Arg Val
1955 1960 1965

Glu Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Thr
1970 1975 1980

Asp Gln Gly Phe Asp Val Ile Glu Val Ala Arg Leu Asn Gly Ser
1985 1990 1995

Phe Arg Tyr Val Val Ile Ser Gln Gly Leu Asp Lys Pro Arg Ala
2000 2005 2010

Ile Thr Val His Pro Glu Lys Gly Tyr Leu Phe Trp Thr Glu Trp
2015 2020 2025

Gly His Tyr Pro Arg Ile Glu Arg Ser Arg Leu Asp Gly Thr Glu
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Arg Val Val Leu Val Asn Val Ser Ile Ser Trp Pro Asn Gly Ile
2045 2050 2055

Ser Val Asp Tyr Gln Gly Gly Lys Leu Tyr Trp Cys Asp Ala Arg
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Met Asp Lys Ile Glu Arg Ile Asp Leu Glu Thr Gly Glu Asn Arg
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Glu Val Val Leu Ser Ser Asn Asn Met Asp Met Phe Ser Val Ser
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Val Phe Glu Asp Phe Ile Tyr Trp Ser Asp Arg Thr His Ala Asn
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Gly Ser Ile Lys Arg Gly Cys Lys Asp Asn Ala Thr Asp Ser Val
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Pro Leu Arg Thr Gly Ile Gly Val Gln Leu Lys Asp Ile Lys Val
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Phe Asn Arg Asp Arg Gln Lys Gly Thr Asn Val Cys Ala Val Ala
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Asn Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Gly Gly Gln
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Arg Ala Cys Ala Cys Ala His Gly Met Leu Ala Glu Asp Gly Ala
2180 2185 2190

Ser Cys Arg Glu Tyr Ala Gly Tyr Leu Leu Tyr Ser Glu Arg Thr
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Ile Leu Lys Ser Ile His Leu Ser Asp Glu Arg Asn Leu Asn Ala
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Pro Val Gln Pro Phe Glu Asp Pro Glu His Met Lys Asn Val Ile
2225 2230 2235

Ala Leu Ala Phe Asp Tyr Arg Ala Gly Thr Ser Pro Gly Thr Pro
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Asn Arg Ile Phe Phe Ser Asp Ile His Phe Gly Asn Ile Gln Gln
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Ile Asn Asp Asp Gly Ser Gly Arg Thr Thr Ile Val Glu Asn Val
2270 2275 2280

Gly Ser Val Glu Gly Leu Ala Tyr His Arg Gly Trp Asp Thr Leu
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Tyr Trp Thr Ser Tyr Thr Thr Ser Thr Ile Thr Arg His Thr Val
2300 2305 2310

Asp Gln Thr Arg Pro Gly Ala Phe Glu Arg Glu Thr Val Ile Thr
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Met Ser Gly Asp Asp His Pro Arg Ala Phe Val Leu Asp Glu Cys
2330 2335 2340

Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Leu His Pro Ser
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Ile Met Arg Ala Ala Leu Ser Gly Ala Asn Val Leu Thr Leu Ile
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Glu Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala Ile Asp His Arg
2375 2380 2385

Ala Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp Lys Ile Glu
2390 2395 2400

Arg Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu Lys Ser
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Glu Pro Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His Ile
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Phe Trp Thr Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys
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Tyr Val Gly Ser Asp Met Lys Leu Leu Arg Val Asp Ile Pro Gln
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Gln Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys
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Glu Leu Ser Pro Cys Arg Ile Asn Asn Gly Gly Cys Gln Asp Leu
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Cys Leu Leu Thr His Gln Gly His Val Asn Cys Ser Cys Arg Gly
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Gly Arg Ile Leu Gln Glu Asp Phe Thr Cys Arg Ala Val Asn Ser
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Ser Cys Arg Ala Gln Asp Glu Phe Glu Cys Ala Asn Gly Glu Cys
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Ile Ser Phe Ser Leu Thr Cys Asp Gly Val Ser His Cys Lys Asp
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Lys Thr Phe Arg Gln Cys Asn Asn Gly Arg Cys Val Ser Asn Met
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Leu Trp Cys Asn Gly Val Asp Asp Cys Gly Asp Gly Ser Asp Glu
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Ile Pro Cys Asn Lys Thr Ala Cys Gly Val Gly Glu Phe Arg Cys
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Arg Asp Gly Ser Cys Ile Gly Asn Ser Ser Arg Cys Asn Gln Phe
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Val Asp Cys Glu Asp Ala Ser Asp Glu Met Asn Cys Ser Ala Thr
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Ser Lys Gln Trp Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly
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Ser Phe Ser Cys Pro Gly Thr His Val Cys Val Pro Glu Arg Trp
2780 2785 2790

Leu Cys Asp Gly Asp Lys Asp Cys Thr Asp Gly Ala Asp Glu Ser
2795 2800 2805

Val Thr Ala Gly Cys Leu Tyr Asn Ser Thr Cys Asp Asp Arg Glu
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Phe Met Cys Gln Asn Arg Leu Cys Ile Pro Lys His Phe Val Cys
2825 2830 2835

Asp His Asp Arg Asp Cys Ala Asp Gly Ser Asp Glu Ser Pro Glu
2840 2845 2850

Cys Glu Tyr Pro Thr Cys Gly Pro Asn Glu Phe Arg Cys Ala Asn
2855 2860 2865

Gly Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp Gly Glu Asn
2870 2875 2880

Asp Cys His Asp His Ser Asp Glu Ala Pro Lys Asn Pro His Cys
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Thr Ser Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu Cys
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Ser Ser Gly Arg Cys Val Ala Glu Ala Leu Leu Cys Asn Gly Gln
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Asp Asp Cys Gly Asp Gly Ser Asp Glu Arg Gly Cys His Val Asn
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Glu Cys Leu Ser Arg Lys Leu Ser Gly Cys Ser Gln Asp Cys Glu
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Tyr Lys Cys Leu Cys Val Glu Gly Tyr Ala Pro Arg Gly Gly Asp
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Pro His Ser Cys Lys Ala Val Thr Asp Glu Glu Pro Phe Leu Ile
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Phe Ala Asn Arg Tyr Tyr Leu Arg Lys Leu Asn Leu Asp Gly Ser
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Tyr Val Tyr Trp Thr Asp Trp Glu Thr Lys Ser Ile Asn Arg Ala
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His Lys Thr Thr Gly Ala Asn Lys Thr Leu Leu Ile Ser Thr Leu
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<211> 4544
<212> PRT
<213> HOMO SAPIENS

<400> 68

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Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys Asp
35 40 45

Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu Ala Pro Glu Ile Cys
50 55 60

Pro Gln Ser Lys Ala Gln Arg Cys Gln Pro Asn Glu His Asn Cys Leu
65 70 75 80

Gly Thr Glu Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Val Gln
85 90 95

Asp Cys Met Asp Gly Ser Asp Glu Gly Pro His Cys Arg Glu Leu Gln
100 105 110

Gly Asn Cys Ser Arg Leu Gly Cys Gln His His Cys Val Pro Thr Leu
115 120 125

Asp Gly Pro Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Gln Ala Asp

130 135 140

Gly Lys Thr Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr Cys
145 150 155 160

Ser Gln Leu Cys Thr Asn Thr Asp Gly Ser Phe Ile Cys Gly Cys Val
165 170 175

Glu Gly Tyr Leu Leu Gln Pro Asp Asn Arg Ser Cys Lys Ala Lys Asn
180 185 190

Glu Pro Val Asp Arg Pro Pro Val Leu Leu Ile Ala Asn Ser Gln Asn
195 200 205

Ile Leu Ala Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr Pro
210 215 220

Thr Ser Thr Arg Gln Thr Thr Ala Met Asp Phe Ser Tyr Ala Asn Glu
225 230 235 240

Thr Val Cys Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln Leu
245 250 255

Lys Cys Ala Arg Met Pro Gly Leu Lys Gly Phe Val Asp Glu His Thr
260 265 270

Ile Asn Ile Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile Asp
275 280 285

Trp Leu Thr Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg Ile
290 295 300

Phe Val Cys Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp Leu
305 310 315 320

Glu Leu Tyr Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly Lys
325 330 335

Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys Asp
340 345 350

Met Asp Gly Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val Phe
355 360 365

Pro His Gly Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp Ala
370 375 380

Asp Ala Tyr Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys Gly
385 390 395 400

Arg Gln Thr Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly Leu

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Thr Val Phe Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala Asn
420 425 430

Ala Gln Gln Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser Thr
435 440 445

Glu Tyr Gln Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His Ile
450 455 460

Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu Asn
465 470 475 480

Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu Ala
485 490 495

Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser Leu
500 505 510

Gly Ser Asp Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe Leu
515 520 525

Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met Gly
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Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met Asn
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Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe Ala
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Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu
580 585 590

Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val Ala
595 600 605

Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro Lys
610 615 620

Lys Thr Ile Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg Lys
625 630 635 640

Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val Asp
645 650 655

Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro Lys
660 665 670

Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser His

675 680 685

Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly Leu
690 695 700

Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe Tyr
705 710 715 720

Asp Arg Ile Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile Val
725 730 735

Tyr Glu Gly Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His Gly
740 745 750

Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg Leu
755 760 765

Glu Arg Gly Val Gly Gly Ala Pro Pro Thr Val Thr Leu Leu Arg Ser
770 775 780

Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln Gln
785 790 795 800

Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser Ser
805 810 815

Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu Asp
820 825 830

Gln Val Leu Asp Ala Asp Gly Val Thr Cys Leu Ala Asn Pro Ser Tyr
835 840 845

Val Pro Pro Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser
850 855 860

Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu
865 870 875 880

Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro
885 890 895

Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp
900 905 910

Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn
915 920 925

Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala
930 935 940

Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp

945 950 955 960

Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys
965 970 975

Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile
980 985 990

Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu
995 1000 1005

Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn
1010 1015 1020

Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn
1025 1030 1035

Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn
1040 1045 1050

Gln Ala Thr Arg Pro Pro Gly Gly Cys His Thr Asp Glu Phe Gln
1055 1060 1065

Cys Arg Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys Asp
1070 1075 1080

Gly Asp Thr Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys Glu
1085 1090 1095

Gly Val Thr His Val Cys Asp Pro Ser Val Lys Phe Gly Cys Lys
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Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val Cys Asp Gly Asp
1115 1120 1125

Asn Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys Glu Ser Leu
1130 1135 1140

Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser Val
1145 1150 1155

Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Asn Asp Asp Cys Gly
1160 1165 1170

Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp Gln Cys Ser Leu Asn
1175 1180 1185

Asn Gly Gly Cys Ser His Asn Cys Ser Val Ala Pro Gly Glu Gly
1190 1195 1200

Ile Val Cys Ser Cys Pro Leu Gly Met Glu Leu Gly Pro Asp Asn

1205 1210 1215

His Thr Cys Gln Ile Gln Ser Tyr Cys Ala Lys His Leu Lys Cys
1220 1225 1230

Ser Gln Lys Cys Asp Gln Asn Lys Phe Ser Val Lys Cys Ser Cys
1235 1240 1245

Tyr Glu Gly Trp Val Leu Glu Pro Asp Gly Glu Ser Cys Arg Ser
1250 1255 1260

Leu Asp Pro Phe Lys Pro Phe Ile Ile Phe Ser Asn Arg His Glu
1265 1270 1275

Ile Arg Arg Ile Asp Leu His Lys Gly Asp Tyr Ser Val Leu Val
1280 1285 1290

Pro Gly Leu Arg Asn Thr Ile Ala Leu Asp Phe His Leu Ser Gln
1295 1300 1305

Ser Ala Leu Tyr Trp Thr Asp Val Val Glu Asp Lys Ile Tyr Arg
1310 1315 1320

Gly Lys Leu Leu Asp Asn Gly Ala Leu Thr Ser Phe Glu Val Val
1325 1330 1335

Ile Gln Tyr Gly Leu Ala Thr Pro Glu Gly Leu Ala Val Asp Trp
1340 1345 1350

Ile Ala Gly Asn Ile Tyr Trp Val Glu Ser Asn Leu Asp Gln Ile
1355 1360 1365

Glu Val Ala Lys Leu Asp Gly Thr Leu Arg Thr Thr Leu Leu Ala
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Gly Asp Ile Glu His Pro Arg Ala Ile Ala Leu Asp Pro Arg Asp
1385 1390 1395

Gly Ile Leu Phe Trp Thr Asp Trp Asp Ala Ser Leu Pro Arg Ile
1400 1405 1410

Glu Ala Ala Ser Met Ser Gly Ala Gly Arg Arg Thr Val His Arg
1415 1420 1425

Glu Thr Gly Ser Gly Gly Trp Pro Asn Gly Leu Thr Val Asp Tyr
1430 1435 1440

Leu Glu Lys Arg Ile Leu Trp Ile Asp Ala Arg Ser Asp Ala Ile
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Tyr Ser Ala Arg Tyr Asp Gly Ser Gly His Met Glu Val Leu Arg

1460 1465 1470

Gly His Glu Phe Leu Ser His Pro Phe Ala Val Thr Leu Tyr Gly
1475 1480 1485

Gly Glu Val Tyr Trp Thr Asp Trp Arg Thr Asn Thr Leu Ala Lys
1490 1495 1500

Ala Asn Lys Trp Thr Gly His Asn Val Thr Val Val Gln Arg Thr
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Asn Thr Gln Pro Phe Asp Leu Gln Val Tyr His Pro Ser Arg Gln
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Pro Met Ala Pro Asn Pro Cys Glu Ala Asn Gly Gly Gln Gly Pro
1535 1540 1545

Cys Ser His Leu Cys Leu Ile Asn Tyr Asn Arg Thr Val Ser Cys
1550 1555 1560

Ala Cys Pro His Leu Met Lys Leu His Lys Asp Asn Thr Thr Cys
1565 1570 1575

Tyr Glu Phe Lys Lys Phe Leu Leu Tyr Ala Arg Gln Met Glu Ile
1580 1585 1590

Arg Gly Val Asp Leu Asp Ala Pro Tyr Tyr Asn Tyr Ile Ile Ser
1595 1600 1605

Phe Thr Val Pro Asp Ile Asp Asn Val Thr Val Leu Asp Tyr Asp
1610 1615 1620

Ala Arg Glu Gln Arg Val Tyr Trp Ser Asp Val Arg Thr Gln Ala
1625 1630 1635

Ile Lys Arg Ala Phe Ile Asn Gly Thr Gly Val Glu Thr Val Val
1640 1645 1650

Ser Ala Asp Leu Pro Asn Ala His Gly Leu Ala Val Asp Trp Val
1655 1660 1665

Ser Arg Asn Leu Phe Trp Thr Ser Tyr Asp Thr Asn Lys Lys Gln
1670 1675 1680

Ile Asn Val Ala Arg Leu Asp Gly Ser Phe Lys Asn Ala Val Val
1685 1690 1695

Gln Gly Leu Glu Gln Pro His Gly Leu Val Val His Pro Leu Arg
1700 1705 1710

Gly Lys Leu Tyr Trp Thr Asp Gly Asp Asn Ile Ser Met Ala Asn

1715 1720 1725

Met Asp Gly Ser Asn Arg Thr Leu Leu Phe Ser Gly Gln Lys Gly
1730 1735 1740

Pro Val Gly Leu Ala Ile Asp Phe Pro Glu Ser Lys Leu Tyr Trp
1745 1750 1755

Ile Ser Ser Gly Asn His Thr Ile Asn Arg Cys Asn Leu Asp Gly
1760 1765 1770

Ser Gly Leu Glu Val Ile Asp Ala Met Arg Ser Gln Leu Gly Lys
1775 1780 1785

Ala Thr Ala Leu Ala Ile Met Gly Asp Lys Leu Trp Trp Ala Asp
1790 1795 1800

Gln Val Ser Glu Lys Met Gly Thr Cys Ser Lys Ala Asp Gly Ser
1805 1810 1815

Gly Ser Val Val Leu Arg Asn Ser Thr Thr Leu Val Met His Met
1820 1825 1830

Lys Val Tyr Asp Glu Ser Ile Gln Leu Asp His Lys Gly Thr Asn
1835 1840 1845

Pro Cys Ser Val Asn Asn Gly Asp Cys Ser Gln Leu Cys Leu Pro
1850 1855 1860

Thr Ser Glu Thr Thr Arg Ser Cys Met Cys Thr Ala Gly Tyr Ser
1865 1870 1875

Leu Arg Ser Gly Gln Gln Ala Cys Glu Gly Val Gly Ser Phe Leu
1880 1885 1890

Leu Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro Leu Asp Pro
1895 1900 1905

Asn Asp Lys Ser Asp Ala Leu Val Pro Val Ser Gly Thr Ser Leu
1910 1915 1920

Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr Ile Tyr Trp
1925 1930 1935

Val Asp Met Gly Leu Ser Thr Ile Ser Arg Ala Lys Arg Asp Gln
1940 1945 1950

Thr Trp Arg Glu Asp Val Val Thr Asn Gly Ile Gly Arg Val Glu
1955 1960 1965

Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Thr Asp

1970 1975 1980

Gln Gly Phe Asp Val Ile Glu Val Ala Arg Leu Asn Gly Ser Phe
1985 1990 1995

Arg Tyr Val Val Ile Ser Gln Gly Leu Asp Lys Pro Arg Ala Ile
2000 2005 2010

Thr Val His Pro Glu Lys Gly Tyr Leu Phe Trp Thr Glu Trp Gly
2015 2020 2025

Gln Tyr Pro Arg Ile Glu Arg Ser Arg Leu Asp Gly Thr Glu Arg
2030 2035 2040

Val Val Leu Val Asn Val Ser Ile Ser Trp Pro Asn Gly Ile Ser
2045 2050 2055

Val Asp Tyr Gln Asp Gly Lys Leu Tyr Trp Cys Asp Ala Arg Thr
2060 2065 2070

Asp Lys Ile Glu Arg Ile Asp Leu Glu Thr Gly Glu Asn Arg Glu
2075 2080 2085

Val Val Leu Ser Ser Asn Asn Met Asp Met Phe Ser Val Ser Val
2090 2095 2100

Phe Glu Asp Phe Ile Tyr Trp Ser Asp Arg Thr His Ala Asn Gly
2105 2110 2115

Ser Ile Lys Arg Gly Ser Lys Asp Asn Ala Thr Asp Ser Val Pro
2120 2125 2130

Leu Arg Thr Gly Ile Gly Val Gln Leu Lys Asp Ile Lys Val Phe
2135 2140 2145

Asn Arg Asp Arg Gln Lys Gly Thr Asn Val Cys Ala Val Ala Asn
2150 2155 2160

Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Arg Gly Gln Arg
2165 2170 2175

Ala Cys Ala Cys Ala His Gly Met Leu Ala Glu Asp Gly Ala Ser
2180 2185 2190

Cys Arg Glu Tyr Ala Gly Tyr Leu Leu Tyr Ser Glu Arg Thr Ile
2195 2200 2205

Leu Lys Ser Ile His Leu Ser Asp Glu Arg Asn Leu Asn Ala Pro
2210 2215 2220

Val Gln Pro Phe Glu Asp Pro Glu His Met Lys Asn Val Ile Ala

2225 2230 2235

Leu Ala Phe Asp Tyr Arg Ala Gly Thr Ser Pro Gly Thr Pro Asn
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Arg Ile Phe Phe Ser Asp Ile His Phe Gly Asn Ile Gln Gln Ile
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Asn Asp Asp Gly Ser Arg Arg Ile Thr Ile Val Glu Asn Val Gly
2270 2275 2280

Ser Val Glu Gly Leu Ala Tyr His Arg Gly Trp Asp Thr Leu Tyr
2285 2290 2295

Trp Thr Ser Tyr Thr Thr Ser Thr Ile Thr Arg His Thr Val Asp
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Gln Thr Arg Pro Gly Ala Phe Glu Arg Glu Thr Val Ile Thr Met
2315 2320 2325

Ser Gly Asp Asp His Pro Arg Ala Phe Val Leu Asp Glu Cys Gln
2330 2335 2340

Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Gln His Pro Ser Ile
2345 2350 2355

Met Arg Ala Ala Leu Ser Gly Ala Asn Val Leu Thr Leu Ile Glu
2360 2365 2370

Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala Ile Asp His Arg Ala
2375 2380 2385

Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp Lys Ile Glu Arg
2390 2395 2400

Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu Lys Ser Glu
2405 2410 2415

Pro Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His Ile Phe
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Trp Thr Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys His
2435 2440 2445

Val Gly Ser Asn Met Lys Leu Leu Arg Val Asp Ile Pro Gln Gln
2450 2455 2460

Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys Glu
2465 2470 2475

Leu Ser Pro Cys Arg Ile Asn Asn Gly Gly Cys Gln Asp Leu Cys

2480 2485 2490

Leu Leu Thr His Gln Gly His Val Asn Cys Ser Cys Arg Gly Gly
2495 2500 2505

Arg Ile Leu Gln Asp Asp Leu Thr Cys Arg Ala Val Asn Ser Ser
2510 2515 2520

Cys Arg Ala Gln Asp Glu Phe Glu Cys Ala Asn Gly Glu Cys Ile
2525 2530 2535

Asn Phe Ser Leu Thr Cys Asp Gly Val Pro His Cys Lys Asp Lys
2540 2545 2550

Ser Asp Glu Lys Pro Ser Tyr Cys Asn Ser Arg Arg Cys Lys Lys
2555 2560 2565

Thr Phe Arg Gln Cys Ser Asn Gly Arg Cys Val Ser Asn Met Leu
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Trp Cys Asn Gly Ala Asp Asp Cys Gly Asp Gly Ser Asp Glu Ile
2585 2590 2595

Pro Cys Asn Lys Thr Ala Cys Gly Val Gly Glu Phe Arg Cys Arg
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Asp Gly Thr Cys Ile Gly Asn Ser Ser Arg Cys Asn Gln Phe Val
2615 2620 2625

Asp Cys Glu Asp Ala Ser Asp Glu Met Asn Cys Ser Ala Thr Asp
2630 2635 2640

Cys Ser Ser Tyr Phe Arg Leu Gly Val Lys Gly Val Leu Phe Gln
2645 2650 2655

Pro Cys Glu Arg Thr Ser Leu Cys Tyr Ala Pro Ser Trp Val Cys
2660 2665 2670

Asp Gly Ala Asn Asp Cys Gly Asp Tyr Ser Asp Glu Arg Asp Cys
2675 2680 2685

Pro Gly Val Lys Arg Pro Arg Cys Pro Leu Asn Tyr Phe Ala Cys
2690 2695 2700

Pro Ser Gly Arg Cys Ile Pro Met Ser Trp Thr Cys Asp Lys Glu
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Asp Asp Cys Glu His Gly Glu Asp Glu Thr His Cys Asn Lys Phe
2720 2725 2730

Cys Ser Glu Ala Gln Phe Glu Cys Gln Asn His Arg Cys Ile Ser

2735 2740 2745

Lys Gln Trp Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly Ser
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Asp Glu Ala Ala His Cys Glu Gly Lys Thr Cys Gly Pro Ser Ser
2765 2770 2775

Phe Ser Cys Pro Gly Thr His Val Cys Val Pro Glu Arg Trp Leu
2780 2785 2790

Cys Asp Gly Asp Lys Asp Cys Ala Asp Gly Ala Asp Glu Ser Ile
2795 2800 2805

Ala Ala Gly Cys Leu Tyr Asn Ser Thr Cys Asp Asp Arg Glu Phe
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Met Cys Gln Asn Arg Gln Cys Ile Pro Lys His Phe Val Cys Asp
2825 2830 2835

His Asp Arg Asp Cys Ala Asp Gly Ser Asp Glu Ser Pro Glu Cys
2840 2845 2850

Glu Tyr Pro Thr Cys Gly Pro Ser Glu Phe Arg Cys Ala Asn Gly
2855 2860 2865

Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp Gly Glu Asn Asp
2870 2875 2880

Cys His Asp Gln Ser Asp Glu Ala Pro Lys Asn Pro His Cys Thr
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Ser Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu Cys Ser
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Ser Gly Arg Cys Val Ala Glu Ala Leu Leu Cys Asn Gly Gln Asp
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Asp Cys Gly Asp Ser Ser Asp Glu Arg Gly Cys His Ile Asn Glu
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Cys Leu Ser Arg Lys Leu Ser Gly Cys Ser Gln Asp Cys Glu Asp
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Leu Lys Ile Gly Phe Lys Cys Arg Cys Arg Pro Gly Phe Arg Leu
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Lys Asp Asp Gly Arg Thr Cys Ala Asp Val Asp Glu Cys Ser Thr
2975 2980 2985

Thr Phe Pro Cys Ser Gln Arg Cys Ile Asn Thr His Gly Ser Tyr

2990 2995 3000

Lys Cys Leu Cys Val Glu Gly Tyr Ala Pro Arg Gly Gly Asp Pro
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His Ser Cys Lys Ala Val Thr Asp Glu Glu Pro Phe Leu Ile Phe
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Ala Asn Arg Tyr Tyr Leu Arg Lys Leu Asn Leu Asp Gly Ser Asn
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Tyr Thr Leu Leu Lys Gln Gly Leu Asn Asn Ala Val Ala Leu Asp
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Phe Asp Tyr Arg Glu Gln Met Ile Tyr Trp Thr Asp Val Thr Thr
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Gln Gly Ser Met Ile Arg Arg Met His Leu Asn Gly Ser Asn Val
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Gln Val Leu His Arg Thr Gly Leu Ser Asn Pro Asp Gly Leu Ala
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Val Asp Trp Val Gly Gly Asn Leu Tyr Trp Cys Asp Lys Gly Arg
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Asp Thr Ile Glu Val Ser Lys Leu Asn Gly Ala Tyr Arg Thr Val
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Leu Val Ser Ser Gly Leu Arg Glu Pro Arg Ala Leu Val Val Asp
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Val Gln Asn Gly Tyr Leu Tyr Trp Thr Asp Trp Gly Asp His Ser
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Leu Ile Gly Arg Ile Gly Met Asp Gly Ser Ser Arg Ser Val Ile
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Val Asp Thr Lys Ile Thr Trp Pro Asn Gly Leu Thr Leu Asp Tyr
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Val Thr Glu Arg Ile Tyr Trp Ala Asp Ala Arg Glu Asp Tyr Ile
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Glu Phe Ala Ser Leu Asp Gly Ser Asn Arg His Val Val Leu Ser
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Gln Asp Ile Pro His Ile Phe Ala Leu Thr Leu Phe Glu Asp Tyr
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Val Tyr Trp Thr Asp Trp Glu Thr Lys Ser Ile Asn Arg Ala His

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Lys Thr Thr Gly Thr Asn Lys Thr Leu Leu Ile Ser Thr Leu His
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Arg Pro Met Asp Leu His Val Phe His Ala Leu Arg Gln Pro Asp
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Val Pro Asn His Pro Cys Lys Val Asn Asn Gly Gly Cys Ser Asn
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Leu Cys Leu Leu Ser Pro Gly Gly Gly His Lys Cys Ala Cys Pro
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Thr Asn Phe Tyr Leu Gly Ser Asp Gly Arg Thr Cys Val Ser Asn
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Cys Thr Ala Ser Gln Phe Val Cys Lys Asn Asp Lys Cys Ile Pro
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Pro Cys Ser Glu Ser Glu Phe Ser Cys Ala Asn Gly Arg Cys Ile
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Ala Gly Arg Trp Lys Cys Asp Gly Asp His Asp Cys Ala Asp Gly
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Ser Asp Glu Lys Asp Cys Thr Pro Arg Cys Asp Met Asp Gln Phe
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Gln Cys Lys Ser Gly His Cys Ile Pro Leu Arg Trp Arg Cys Asp
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Thr Gly Val Arg Thr Cys Pro Leu Asp Glu Phe Gln Cys Asn Asn
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Thr Leu Cys Lys Pro Leu Ala Trp Lys Cys Asp Gly Glu Asp Asp
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Asp Gly Thr Asp Glu Glu Asp Cys Glu Pro Pro Thr Ala His Thr
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Thr His Cys Lys Asp Lys Lys Glu Phe Leu Cys Arg Asn Gln Arg
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Cys Leu Ser Ser Ser Leu Arg Cys Asn Met Phe Asp Asp Cys Gly

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Asp Gly Ser Asp Glu Glu Asp Cys Ser Ile Asp Pro Lys Leu Thr
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Ser Cys Ala Thr Asn Ala Ser Ile Cys Gly Asp Glu Ala Arg Cys
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Val Arg Thr Glu Lys Ala Ala Tyr Cys Ala Cys Arg Ser Gly Phe
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His Thr Val Pro Gly Gln Pro Gly Cys Gln Asp Ile Asn Glu Cys
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Leu Arg Phe Gly Thr Cys Ser Gln Leu Cys Asn Asn Thr Lys Gly
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Gly His Leu Cys Ser Cys Ala Arg Asn Phe Met Lys Thr His Asn
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Trp His Thr Gly Thr Ile Ser Tyr Arg Ser Leu Pro Pro Ala Ala
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Pro Pro Thr Thr Ser Asn Arg His Arg Arg Gln Ile Asp Arg Gly
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Val Thr His Leu Asn Ile Ser Gly Leu Lys Met Pro Arg Gly Ile
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Arg Asp Val Ile Glu Val Ala Gln Met Lys Gly Glu Asn Arg Lys
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Lys Ile His Lys Phe Gly His Ser Pro Leu Val Asn Leu Thr Gly
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Gly Lys Arg Leu Asp Asn Gly Thr Cys Val Pro Val Pro Ser Pro
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Cys Phe Asn Gly Gly Ser Cys Phe Leu Asn Ala Arg Arg Gln Pro
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Asp Gln Cys Trp Glu His Cys Arg Asn Gly Gly Thr Cys Ala Ala
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Ser Pro Ser Gly Met Pro Thr Cys Arg Cys Pro Thr Gly Phe Thr
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Gly Pro Lys Cys Thr Gln Gln Val Cys Ala Gly Tyr Cys Ala Asn

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Asn Ser Thr Cys Thr Val Asn Gln Gly Asn Gln Pro Gln Cys Arg
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Ser Gly Tyr Cys Glu Asn Phe Gly Thr Cys Gln Met Ala Ala Asp
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Gly Gly Ser Cys Thr Met Asn Ser Lys Met Met Pro Glu Cys Gln
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Cys Pro Pro His Met Thr Gly Pro Arg Cys Glu Glu His Val Phe
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Ser Gln Gln Gln Pro Gly His Ile Ala Ser Ile Leu Ile Pro Leu
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Leu Leu Leu Leu Leu Leu Val Leu Val Ala Gly Val Val Phe Trp
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Tyr Lys Arg Arg Val Gln Gly Ala Lys Gly Phe Gln His Gln Arg
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Met Thr Asn Gly Ala Met Asn Val Glu Ile Gly Asn Pro Thr Tyr
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Lys Met Tyr Glu Gly Gly Glu Pro Asp Asp Val Gly Gly Leu Leu
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Asp Ala Asp Phe Ala Leu Asp Pro Asp Lys Pro Thr Asn Phe Thr
4490 4495 4500

Asn Pro Val Tyr Ala Thr Leu Tyr Met Gly Gly His Gly Ser Arg
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<213> MOUSE

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Asp Pro Gly Glu Phe Leu Cys His Asp His Val Thr Cys Val Ser Gln
35 40 45

Ser Trp Leu Cys Asp Gly Asp Pro Asp Cys Pro Asp Gln Ser Asp Glu
50 55 60

Ser Leu Asp Thr Cys Pro Glu Glu Val Glu Ile Lys Cys Pro Leu Asn
65 70 75 80

His Ile Ala Cys His Gly Ser Ser Ala Cys Val His Leu Ser Lys Leu
85 90 95

Cys Asn Gly Val Val Asp Cys Pro Asp Gly Phe Asp Glu Gly Gly His
100 105 110

Cys Gln Glu Leu Leu Pro Ser Cys Gln Gln Leu Asn Cys Gln Phe Lys
115 120 125

Cys Ala Met Val Arg Asn Ala Thr Arg Cys Tyr Cys Glu Asp Gly Phe
130 135 140

Glu Val Ala Glu Asp Gly Arg Ser Cys Lys Asp Gln Asp Glu Cys Ser
145 150 155 160

Ile Tyr Gly Ile Cys Ser Gln Thr Cys Lys Asn Thr Tyr Gly Ser Tyr
165 170 175

Ala Cys Ser Cys Val Glu Gly Tyr Ile Met Gln Ser Asp Asn Arg Ser
180 185 190

Cys Lys Val Lys His Glu Pro Thr Asp Lys Ala Pro Met Leu Leu Ile
195 200 205

Ser Ser Leu Glu Thr Ile Glu Leu Phe Tyr Ile Asn Gly Ser Lys Met
210 215 220

Thr Thr Leu Ser Ser Ala Asn Arg Asn Glu Ile His Thr Leu Asp Phe
225 230 235 240

Ile Tyr Ser Glu Glu Met Ile Cys Trp Ile Glu Ser Arg Glu Ser Ser
245 250 255

Asn Gln Leu Lys Cys Gly Gln Ile Thr Lys Ala Gly Arg Leu Thr Asp
260 265 270

Gln Arg Ile Ile Asn Ser Leu Gln Ser Phe Gln Asn Val Glu Gln Met
275 280 285

Ala Phe Asp Trp Leu Thr Arg Asn Ile Tyr Phe Val Asp His Val Ser
290 295 300

Asp Arg Ile Phe Val Cys Asn Phe Asn Gly Ser Val Cys Val Thr Leu
305 310 315 320

Ile Glu Ser Glu Leu His Asn Pro Lys Ala Ile Ala Ala Asp Pro Ile
325 330 335

Ala Gly Lys Leu Phe Phe Thr Asp Tyr Gly Asn Val Pro Lys Ile Glu
340 345 350

Arg Cys Asp Leu Asp Gly Met Asn Arg Thr Arg Ile Val Tyr Ser Lys
355 360 365

Ala Glu Gln Pro Ser Ala Leu Ala Leu Asp Leu Val Asn Arg Leu Val
370 375 380

Tyr Trp Val Asp Leu Tyr Leu Asp Tyr Val Gly Val Val Asp Tyr Gln
385 390 395 400

Gly Lys Asn Arg His Thr Ile Val Gln Gly Arg Gln Val Lys His Leu
405 410 415

Tyr Gly Ile Thr Val Phe Glu Asp Tyr Leu Tyr Ala Thr Ser Ser Asp
420 425 430

Asn Phe Asn Ile Ile Arg Ile Asn Arg Phe Asn Gly Thr Asp Ile His
435 440 445

Ser Ile Ile Lys Met Glu Ser Ala Arg Gly Ile Arg Thr Tyr Gln Lys
450 455 460

Arg Thr Gln Pro Thr Val Arg Ser His Ala Cys Glu Val Asp Ala Tyr
465 470 475 480

Gly Met Pro Gly Gly Cys Ser His Ile Cys Leu Leu Ser Ser Ser Tyr
485 490 495

Lys Thr Arg Thr Cys Arg Cys Arg Thr Gly Phe Asn Met Gly Ser Asp
500 505 510

Gly Arg Ser Cys Lys Arg Pro Lys Asn Glu Leu Phe Leu Phe Tyr Gly
515 520 525

Lys Gly Arg Pro Gly Ile Val Arg Gly Met Asp Leu Asn Thr Lys Ile
530 535 540

Ala Asp Glu Cys Met Ile Pro Ile Glu Asn Leu Val Asn Pro Arg Ala
545 550 555 560

Leu Asp Phe His Ala Glu Ala Asn Tyr Ile Tyr Phe Ala Asp Thr Thr
565 570 575

Ser Phe Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu Arg Glu Thr
580 585 590

Ile Leu Lys Asp Asp Leu Asp Asn Val Glu Gly Ile Ala Val Asp Trp
595 600 605

Ile Gly Asn Asn Leu Tyr Trp Thr Asn Asp Gly His Arg Lys Thr Ile
610 615 620

Asn Val Ala Arg Leu Glu Lys Ala Ser Gln Ser Arg Lys Thr Leu Leu
625 630 635 640

Glu Gly Gly Met Ser His Pro Arg Ala Ile Val Val Asp Pro Val Asn
645 650 655

Gly Trp Met Tyr Trp Thr Asp Trp Lys Glu Asp Lys Ile Asp Asp Ser
660 665 670

Val Gly Arg Ile Glu Lys Ala Trp Met Asp Gly Val Asn Arg Gln Val
675 680 685

Phe Val Thr Ser Lys Met Leu Trp Pro Asn Gly Leu Thr Leu Asp Phe
690 695 700

His Thr Ser Thr Leu Tyr Trp Cys Asp Ala Tyr Tyr Asp His Ile Glu
705 710 715 720

Lys Val Phe Leu Asn Gly Thr His Arg Lys Val Val Tyr Ser Gly Lys
725 730 735

Glu Leu Asn His Pro Phe Gly Leu Ser His His Gly Asn Tyr Val Phe
740 745 750

Trp Thr Asp Tyr Met Asn Gly Ser Ile Phe Gln Leu Asp Leu Met Thr
755 760 765

Asn Glu Val Thr Leu Leu Arg His Glu Arg Ala Pro Leu Phe Gly Leu
770 775 780

Gln Ile Tyr Asp Pro Arg Lys Gln Gln Gly Asp Asn Met Cys Arg Ile
785 790 795 800

Asn Asn Gly Gly Cys Gly Thr Leu Cys Leu Ala Ile Pro Ala Gly Arg
805 810 815

Val Cys Ala Cys Ala Asp Asn Gln Leu Leu Asp Glu Asn Gly Thr Thr
820 825 830

Cys Thr Phe Asn Pro Glu Glu Ile Arg Phe His Ile Cys Lys Pro Gly
835 840 845

Glu Phe Arg Cys Lys Asn Lys His Cys Ile Gln Ala Arg Trp Lys Cys
850 855 860

Asp Gly Asp Asp Asp Cys Leu Asp Gly Ser Asp Glu Asp Ser Val Thr
865 870 875 880

Cys Phe Asn His Ser Cys Pro Asp Asp Gln Phe Lys Cys Gln Asn Asn
885 890 895

Arg Cys Ile Pro Lys Arg Trp Leu Cys Asp Gly Ala Asn Asp Cys Gly
900 905 910

Ser Asn Glu Asp Glu Ser Asn Gln Thr Cys Thr Ala Arg Thr Cys Gln
915 920 925

Ala Asp Gln Phe Ser Cys Gly Asn Gly Arg Cys Ile Pro Thr Ala Trp
930 935 940

Leu Cys Asp Arg Glu Asp Asp Cys Gly Asp Gln Thr Asp Glu Val Ala
945 950 955 960

Ser Cys Glu Phe Pro Thr Cys Glu Pro Leu Thr Gln Phe Ile Cys Lys
965 970 975

Ser Gly Arg Cys Ile Ser Asn Lys Trp His Cys Asp Thr Asp Asp Asp
980 985 990

Cys Gly Asp Arg Ser Asp Glu Val Gly Cys Val His Ser Cys Leu Asp
995 1000 1005

Asp Gln Phe Arg Cys Ser Ser Gly Arg Cys Ile Pro Gly His Trp
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Ala Cys Asp Gly Asp Asn Asp Cys Gly Asp Phe Ser Asp Glu Thr
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His Ile Asn Cys Thr Lys Glu Glu Ala Arg Ser Pro Ala Gly Cys
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Ile Gly Asn Glu Phe Gln Cys Arg Pro Asp Gly Asn Cys Ile Pro
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Asp Leu Trp Arg Cys Asp Gly Glu Lys Asp Cys Glu Asp Gly Ser
1070 1075 1080

Asp Glu Lys Gly Cys Asn Gly Thr Ile Arg Leu Cys Asp His Lys
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Thr Lys Phe Ser Cys Arg Ser Thr Gly Arg Cys Ile Asn Asn Ala
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Trp Val Cys Asp Gly Asp Val Asp Cys Glu Asp Gln Ser Asp Glu
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Glu Asp Cys Asp Ser Phe Leu Cys Gly Pro Pro Lys Tyr Pro Cys
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Ala Asn Asp Thr Ser Val Cys Leu Gln Pro Glu Lys Leu Cys Asn
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Gly Arg Lys Asp Cys Pro Asp Gly Ser Asp Glu Gly Asp Leu Cys
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Asp Glu Cys Ser Leu Asn Asn Gly Gly Cys Ser Asn His Cys Ser
1175 1180 1185

Val Val Pro Gly Arg Gly Ile Val Cys Ser Cys Pro Glu Gly His
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Gln Leu Lys Lys Asp Asn Arg Thr Cys Glu Ile Val Asp Tyr Cys
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Ala Ser His Leu Arg Cys Ser Gln Val Cys Glu Gln Gln Lys His
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Met Val Lys Cys Ser Cys Tyr Glu Gly Trp Ala Leu Gly Thr Asp
1235 1240 1245

Gly Glu Ser Cys Thr Ser Val Asp Ser Phe Glu Ala Phe Ile Ile
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Phe Ser Ile Arg His Glu Ile Arg Arg Ile Asp Leu His Lys Gly
1265 1270 1275

Asp Tyr Ser Leu Leu Val Pro Gly Leu Arg Asn Thr Ile Ala Leu
1280 1285 1290

Asp Phe His Phe Asn Gln Ser Leu Leu Tyr Trp Thr Asp Val Val
1295 1300 1305

Glu Asp Arg Ile Tyr Arg Gly Lys Leu Ser Glu Ser Gly Gly Val
1310 1315 1320

Ser Ala Ile Glu Val Val Val Glu His Gly Leu Ala Thr Pro Glu
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Gly Leu Thr Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Ile Asp
1340 1345 1350

Ser Asn Leu Asp Gln Ile Glu Val Ser Lys Leu Asp Gly Ser Leu
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Arg Ala Thr Leu Ile Ala Gly Ala Met Glu His Pro Arg Ala Ile
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Ala Leu Asp Pro Arg Tyr Gly Ile Leu Phe Trp Thr Asp Trp Asp
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Ala Asn Phe Pro Arg Ile Glu Ser Ala Ser Met Ser Gly Ala Gly
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Arg Lys Thr Ile Tyr Lys Asp Met Lys Thr Gly Ala Trp Pro Asn
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Gly Leu Thr Val Asp His Phe Glu Arg Arg Ile Val Trp Thr Asp
1430 1435 1440

Ala Arg Ser Asp Ala Ile Tyr Ser Ala Phe Tyr Asp Gly Thr Asn
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Met Ile Glu Ile Ile Arg Gly His Glu Tyr Leu Ser His Pro Phe
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Ala Val Ser Leu Tyr Gly Ser Glu Val Tyr Trp Thr Asp Trp Arg
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Thr Asn Thr Leu Ala Lys Ala Asn Lys Trp Thr Gly Gln Asn Val
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Ser Val Ile Gln Lys Thr Ser Ala Gln Pro Phe Asp Leu Gln Ile
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Gly Leu Glu Thr Val Ile Ser Arg Asp Ile Gln Ser Ile Arg Gly
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Leu Ala Val Asp Trp Val Ser Arg Asn Leu Tyr Trp Ile Ser Ser
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Glu Phe Asp Glu Thr Gln Ile Asn Val Ala Arg Leu Asp Gly Ser
1670 1675 1680

Leu Lys Thr Ser Ile Ile His Gly Ile Asp Lys Pro Gln Cys Leu
1685 1690 1695

Ala Ala His Pro Val Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asn
1700 1705 1710

Thr Ile Asn Met Ala Asn Met Asp Gly Ser Asn Ser Lys Ile Leu
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Phe Gln Asn Gln Lys Glu Pro Val Gly Leu Ser Ile Asp Tyr Val
1730 1735 1740

Glu Asn Lys Leu Tyr Trp Ile Ser Ser Gly Asn Gly Thr Ile Asn
1745 1750 1755

Arg Cys Asn Leu Asp Gly Gly Asn Leu Glu Val Ile Glu Ser Met
1760 1765 1770

Lys Glu Glu Leu Thr Lys Ala Thr Ala Leu Thr Ile Met Asp Lys
1775 1780 1785

Lys Leu Trp Trp Ala Asp Gln Asn Leu Ala Gln Leu Gly Thr Cys
1790 1795 1800

Asn Lys Arg Asp Gly Arg Asn Pro Ser Ile Leu Arg Asn Lys Thr
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Ser Gly Val Val His Met Lys Val Tyr Asp Lys Glu Ala Gln Gln
1820 1825 1830

Gly Ser Asn Ser Cys Gln Val Asn Asn Gly Gly Cys Ser Gln Leu
1835 1840 1845

Cys Leu Pro Thr Ser Glu Thr Thr Arg Thr Cys Met Cys Thr Val
1850 1855 1860

Gly Tyr Tyr Leu Gln Lys Asn Arg Met Ser Cys Gln Gly Ile Glu
1865 1870 1875

Ser Phe Leu Met Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro
1880 1885 1890

Leu Glu Pro Arg Asp Lys Val Asp Ala Leu Met Pro Ile Ser Gly
1895 1900 1905

Ala Ala Phe Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr
1910 1915 1920

Ile Tyr Trp Thr Asp Met Gly Leu Asn Lys Ile Ser Arg Ala Lys
1925 1930 1935

Arg Asp Gln Thr Trp Lys Glu Asp Val Val Thr Asn Gly Leu Gly
1940 1945 1950

Arg Val Glu Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr
1955 1960 1965

Trp Thr Asp His Gly Phe Asn Leu Ile Glu Val Ala Arg Leu Asn
1970 1975 1980

Gly Ser Phe Arg Tyr Val Ile Ile Ser Gln Gly Leu Asp Gln Pro
1985 1990 1995

Arg Ser Ile Ala Val His Pro Glu Lys Gly Phe Leu Phe Trp Thr
2000 2005 2010

Glu Trp Gly Gln Val Pro Cys Ile Gly Lys Ala Arg Leu Asp Gly
2015 2020 2025

Ser Glu Lys Val Met Ile Val Ser Val Gly Ile Thr Trp Pro Asn
2030 2035 2040

Gly Ile Ser Ile Asp Tyr Glu Glu Asn Lys Leu Tyr Trp Cys Asp
2045 2050 2055

Ala Arg Ser Asp Lys Ile Glu Arg Ile Asp Leu Asp Thr Gly Ala
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Asn Arg Glu Val Leu Leu Ser Gly Ser Asn Val Asp Leu Phe Ser
2075 2080 2085

Val Ala Val Phe Gly Ala Tyr Ile Tyr Trp Ser Asp Arg Ala His
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Ala Asn Gly Ser Val Arg Arg Gly His Lys Asn Asp Ala Thr Glu
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Thr Val Thr Met Arg Thr Gly Leu Gly Val Asn Leu Lys Glu Ile
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Lys Ile Phe Asn Arg Val Arg Glu Lys Gly Thr Asn Val Cys Ala
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Lys Glu Asn Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Asn
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Ser Arg Arg Thr Cys Ala Cys Ala His Gly Tyr Leu Ala Gly Asp
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Gly Val Thr Cys Leu Arg His Glu Gly Tyr Leu Leu Tyr Ser Gly
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Arg Thr Ile Leu Lys Ser Ile His Leu Ser Asp Glu Thr Asn Leu
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Asn Ser Pro Val Arg Pro Tyr Glu Asn Pro Asn Tyr Phe Lys Asn
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Ile Ile Ala Leu Ala Phe Asp Tyr Asn Gln Arg Arg Glu Gly Thr
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Asn Arg Ile Phe Tyr Ser Asp Ala His Phe Gly Asn Ile Gln Leu
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Ile Lys Asp Asn Trp Glu Asp Arg Gln Val Ile Val Glu Asn Val
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Gly Ser Val Glu Gly Leu Ala Tyr His Arg Ala Trp Asp Thr Leu
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Tyr Trp Thr Ser Ser Ser Thr Ser Ser Ile Thr Arg His Thr Val
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Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Gln His Pro Ser
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Ile Met Arg Ala Thr Leu Thr Gly Lys Asn Ala His Val Val Val
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Tyr Thr Gly Gly Glu Thr Lys Ile Leu Arg Ser Asp Ile Pro His
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Gln Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys
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Glu Leu Ser Pro Cys Ala Leu Leu Asn Gly Gly Cys His Asp Leu
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Cys Leu Leu Thr Pro Asp Gly Arg Val Asn Cys Ser Cys Arg Gly
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Asp Arg Val Leu Leu Ala Asn Asn Arg Cys Val Thr Lys Asn Ser
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Ser Cys Asn Ile Tyr Ser Glu Phe Glu Cys Gly Asn Gly Asp Cys
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Val Asp Tyr Val Leu Thr Cys Asp Gly Ile Pro His Cys Lys Asp
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Lys Ser Asp Glu Lys Leu Leu Tyr Cys Glu Asn Arg Ser Cys Arg
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Ser Gly Phe Lys Pro Cys Tyr Asn Arg Arg Cys Val Pro His Gly
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Lys Leu Cys Asp Gly Thr Asn Asp Cys Gly Asp Ser Ser Asp Glu
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Ala Asp Gly Thr Cys Ile Pro Arg Ser Ala Arg Cys Asn Gln Asn
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Met Asp Cys Ser Asp Ala Ser Asp Glu Lys Gly Cys Asn Asn Thr
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Asp Cys Thr His Phe Tyr Lys Leu Gly Val Lys Ser Thr Gly Phe
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Ile Arg Cys Asn Ser Thr Ser Leu Cys Val Leu Pro Ser Trp Ile
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Cys Asp Gly Ser Asn Asp Cys Gly Asp Tyr Ser Asp Glu Leu Lys
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Cys Pro Val Gln Asn Lys His Lys Cys Glu Glu Asn Tyr Phe Gly
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Cys Pro Ser Gly Arg Cys Ile Leu Asn Thr Trp Val Cys Asp Gly
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Ser Lys His Trp Ile Cys Asp Gly Glu Asp Asp Cys Gly Asp Ser
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Cys Arg Ser Ala Glu His Ser Cys Asn Ser Ser Phe Phe Met Cys
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Asp Asp Cys Gly Asp Gly Ser Asp Glu Thr Asn Cys His Ile Asn
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Glu Cys Leu Ser Lys Lys Ile Ser Gly Cys Ser Gln Asp Cys Gln
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Asp Leu Pro Val Ser Tyr Lys Cys Lys Cys Trp Pro Gly Phe Gln
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Leu Lys Asp Asp Gly Lys Thr Cys Val Asp Ile Asp Glu Cys Ser
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Ser Gly Phe Pro Cys Ser Gln Gln Cys Ile Asn Thr Tyr Gly Thr
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Tyr Lys Cys His Cys Ala Glu Gly Tyr Glu Thr Gln Pro Asp Asn
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Pro Asn Gly Cys Arg Ser Leu Ser Asp Glu Glu Pro Phe Leu Ile
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Leu Ala Asp Gln His Glu Ile Arg Lys Ile Ser Thr Asp Gly Ser
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Asp Phe Asp Tyr Arg Glu Glu Phe Ile Tyr Trp Ile Asp Ser Ser
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Arg Pro Asn Gly Ser Arg Ile Asn Arg Met Cys Leu Asn Gly Ser
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Leu Thr Cys Glu Asn Gly Gly Arg Cys Ile Leu Asn Glu Lys Gly
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Glu Val Asn His Cys Ser Asn Tyr Cys Gln Asn Gly Gly Thr Cys
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His Asn Gly Gly Ser Cys Val Val Thr Ala Gly Asn Gln Pro Tyr
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<213> MOUSE

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Asp Pro Gly Glu Phe Leu Cys His Asp His Val Thr Cys Val Ser Gln
35 40 45

Ser Trp Leu Cys Asp Gly Asp Pro Asp Cys Pro Asp Gln Ser Asp Glu
50 55 60

Ser Leu Asp Thr Cys Pro Glu Glu Val Glu Ile Lys Cys Pro Leu Asn
65 70 75 80

His Ile Ala Cys His Gly Ser Ser Ala Cys Val His Leu Ser Lys Leu
85 90 95

Cys Asn Gly Val Val Asp Cys Pro Asp Gly Phe Asp Glu Gly Gly His
100 105 110

Cys Gln Glu Leu Leu Pro Ser Cys Gln Gln Leu Asn Cys Gln Phe Lys
115 120 125

Cys Ala Met Val Arg Asn Ala Thr Arg Cys Tyr Cys Glu Asp Gly Phe
130 135 140

Glu Val Ala Glu Asp Gly Arg Ser Cys Lys Asp Gln Asp Glu Cys Ser
145 150 155 160

Ile Tyr Gly Ile Cys Ser Gln Thr Cys Lys Asn Thr Tyr Gly Ser Tyr
165 170 175

Ala Cys Ser Cys Val Glu Gly Tyr Ile Met Gln Ser Asp Asn Arg Ser
180 185 190

Cys Lys Val Lys His Glu Pro Thr Asp Lys Ala Pro Met Leu Leu Ile
195 200 205

Ser Ser Leu Glu Thr Ile Glu Leu Phe Tyr Ile Asn Gly Ser Lys Met
210 215 220

Thr Thr Leu Ser Ser Ala Asn Arg Asn Glu Ile His Thr Leu Asp Phe
225 230 235 240

Ile Tyr Ser Glu Glu Met Ile Cys Trp Ile Glu Ser Arg Glu Ser Ser
245 250 255

Asn Gln Leu Lys Cys Gly Gln Ile Thr Lys Ala Gly Arg Leu Thr Asp
260 265 270

Gln Arg Ile Ile Asn Ser Leu Gln Ser Phe Gln Asn Val Glu Gln Met
275 280 285

Ala Phe Asp Trp Leu Thr Arg Asn Ile Tyr Phe Val Asp His Val Ser
290 295 300

Asp Arg Ile Phe Val Cys Asn Phe Asn Gly Ser Val Cys Val Thr Leu
305 310 315 320

Ile Glu Ser Glu Leu His Asn Pro Lys Ala Ile Ala Ala Asp Pro Ile
325 330 335

Ala Gly Lys Leu Phe Phe Thr Asp Tyr Gly Asn Val Pro Lys Ile Glu
340 345 350

Arg Cys Asp Leu Asp Gly Met Asn Arg Thr Arg Ile Val Tyr Ser Lys
355 360 365

Ala Glu Gln Pro Ser Ala Leu Ala Leu Asp Leu Val Asn Arg Leu Val
370 375 380

Tyr Trp Val Asp Leu Tyr Leu Asp Tyr Val Gly Val Val Asp Tyr Gln
385 390 395 400

Gly Lys Asn Arg His Thr Ile Val Gln Gly Arg Gln Val Lys His Leu
405 410 415

Tyr Gly Ile Thr Val Phe Glu Asp Tyr Leu Tyr Ala Thr Ser Ser Asp
420 425 430

Asn Phe Asn Ile Ile Arg Ile Asn Arg Phe Asn Gly Thr Asp Ile His
435 440 445

Ser Ile Ile Lys Met Glu Ser Ala Arg Gly Ile Arg Thr Tyr Gln Lys
450 455 460

Arg Thr Gln Pro Thr Val Arg Ser His Ala Cys Glu Val Asp Ala Tyr
465 470 475 480

Gly Met Pro Gly Gly Cys Ser His Ile Cys Leu Leu Ser Ser Ser Tyr
485 490 495

Lys Thr Arg Thr Cys Arg Cys Arg Thr Gly Phe Asn Met Gly Ser Asp
500 505 510

Gly Arg Ser Cys Lys Arg Pro Lys Asn Glu Leu Phe Leu Phe Tyr Gly
515 520 525

Lys Gly Arg Pro Gly Ile Val Arg Gly Met Asp Leu Asn Thr Lys Ile
530 535 540

Ala Asp Glu Cys Met Ile Pro Ile Glu Asn Leu Val Asn Pro Arg Ala
545 550 555 560

Leu Asp Phe His Ala Glu Ala Asn Tyr Ile Tyr Phe Ala Asp Thr Thr
565 570 575

Ser Phe Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu Arg Glu Thr
580 585 590

Ile Leu Lys Asp Asp Leu Asp Asn Val Glu Gly Ile Ala Val Asp Trp
595 600 605

Ile Gly Asn Asn Leu Tyr Trp Thr Asn Asp Gly His Arg Lys Thr Ile
610 615 620

Asn Val Ala Arg Leu Glu Lys Ala Ser Gln Ser Arg Lys Thr Leu Leu
625 630 635 640

Glu Gly Gly Met Ser His Pro Arg Ala Ile Val Val Asp Pro Val Asn
645 650 655

Gly Trp Met Tyr Trp Thr Asp Trp Lys Glu Asp Lys Ile Asp Asp Ser
660 665 670

Val Gly Arg Ile Glu Lys Ala Trp Met Asp Gly Val Asn Arg Gln Val
675 680 685

Phe Val Thr Ser Lys Met Leu Trp Pro Asn Gly Leu Thr Leu Asp Phe
690 695 700

His Thr Ser Thr Leu Tyr Trp Cys Asp Ala Tyr Tyr Asp His Ile Glu
705 710 715 720

Lys Val Phe Leu Asn Gly Thr His Arg Lys Val Val Tyr Ser Gly Lys
725 730 735

Glu Leu Asn His Pro Phe Gly Leu Ser His His Gly Asn Tyr Val Phe
740 745 750

Trp Thr Asp Tyr Met Asn Gly Ser Ile Phe Gln Leu Asp Leu Met Thr
755 760 765

Asn Glu Val Thr Leu Leu Arg His Glu Arg Ala Pro Leu Phe Gly Leu
770 775 780

Gln Ile Tyr Asp Pro Arg Lys Gln Gln Gly Asp Asn Met Cys Arg Ile
785 790 795 800

Asn Asn Gly Gly Cys Gly Thr Leu Cys Leu Ala Ile Pro Ala Gly Arg
805 810 815

Val Cys Ala Cys Ala Asp Asn Gln Leu Leu Asp Glu Asn Gly Thr Thr
820 825 830

Cys Thr Phe Asn Pro Glu Glu Ile Arg Phe His Ile Cys Lys Pro Gly
835 840 845

Glu Phe Arg Cys Lys Asn Lys His Cys Ile Gln Ala Arg Trp Lys Cys
850 855 860

Asp Gly Asp Asp Asp Cys Leu Asp Gly Ser Asp Glu Asp Ser Val Thr
865 870 875 880

Cys Phe Asn His Ser Cys Pro Asp Asp Gln Phe Lys Cys Gln Asn Asn
885 890 895

Arg Cys Ile Pro Lys Arg Trp Leu Cys Asp Gly Ala Asn Asp Cys Gly
900 905 910

Ser Asn Glu Asp Glu Ser Asn Gln Thr Cys Thr Ala Arg Thr Cys Gln
915 920 925

Ala Asp Gln Phe Ser Cys Gly Asn Gly Arg Cys Ile Pro Thr Ala Trp
930 935 940

Leu Cys Asp Arg Glu Asp Asp Cys Gly Asp Gln Thr Asp Glu Val Ala
945 950 955 960

Ser Cys Glu Phe Pro Thr Cys Glu Pro Leu Thr Gln Phe Ile Cys Lys
965 970 975

Ser Gly Arg Cys Ile Ser Asn Lys Trp His Cys Asp Thr Asp Asp Asp
980 985 990

Cys Gly Asp Arg Ser Asp Glu Val Gly Cys Val His Ser Cys Leu Asp
995 1000 1005

Asp Gln Phe Arg Cys Ser Ser Gly Arg Cys Ile Pro Gly His Trp
1010 1015 1020

Ala Cys Asp Gly Asp Asn Asp Cys Gly Asp Phe Ser Asp Glu Thr
1025 1030 1035

His Ile Asn Cys Thr Lys Glu Glu Ala Arg Ser Pro Ala Gly Cys
1040 1045 1050

Ile Gly Asn Glu Phe Gln Cys Arg Pro Asp Gly Asn Cys Ile Pro
1055 1060 1065

Asp Leu Trp Arg Cys Asp Gly Glu Lys Asp Cys Glu Asp Gly Ser
1070 1075 1080

Asp Glu Lys Gly Cys Asn Gly Thr Ile Arg Leu Cys Asp His Lys
1085 1090 1095

Thr Lys Phe Ser Cys Arg Ser Thr Gly Arg Cys Ile Asn Asn Ala
1100 1105 1110

Trp Val Cys Asp Gly Asp Val Asp Cys Glu Asp Gln Ser Asp Glu
1115 1120 1125

Glu Asp Cys Asp Ser Phe Leu Cys Gly Pro Pro Lys Tyr Pro Cys
1130 1135 1140

Ala Asn Asp Thr Ser Val Cys Leu Gln Pro Glu Lys Leu Cys Asn
1145 1150 1155

Gly Arg Lys Asp Cys Pro Asp Gly Ser Asp Glu Gly Asp Leu Cys
1160 1165 1170

Asp Glu Cys Ser Leu Asn Asn Gly Gly Cys Ser Asn His Cys Ser
1175 1180 1185

Val Val Pro Gly Arg Gly Ile Val Cys Ser Cys Pro Glu Gly His
1190 1195 1200

Gln Leu Lys Lys Asp Asn Arg Thr Cys Glu Ile Val Asp Tyr Cys
1205 1210 1215

Ala Ser His Leu Arg Cys Ser Gln Val Cys Glu Gln Gln Lys His
1220 1225 1230

Met Val Lys Cys Ser Cys Tyr Glu Gly Trp Ala Leu Gly Thr Asp
1235 1240 1245

Gly Glu Ser Cys Thr Ser Val Asp Ser Phe Glu Ala Phe Ile Ile
1250 1255 1260

Phe Ser Ile Arg His Glu Ile Arg Arg Ile Asp Leu His Lys Gly
1265 1270 1275

Asp Tyr Ser Leu Leu Val Pro Gly Leu Arg Asn Thr Ile Ala Leu
1280 1285 1290

Asp Phe His Phe Asn Gln Ser Leu Leu Tyr Trp Thr Asp Val Val
1295 1300 1305

Glu Asp Arg Ile Tyr Arg Gly Lys Leu Ser Glu Ser Gly Gly Val
1310 1315 1320

Ser Ala Ile Glu Val Val Val Glu His Gly Leu Ala Thr Pro Glu
1325 1330 1335

Gly Leu Thr Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Ile Asp
1340 1345 1350

Ser Asn Leu Asp Gln Ile Glu Val Ser Lys Leu Asp Gly Ser Leu
1355 1360 1365

Arg Ala Thr Leu Ile Ala Gly Ala Met Glu His Pro Arg Ala Ile
1370 1375 1380

Ala Leu Asp Pro Arg Tyr Gly Ile Leu Phe Trp Thr Asp Trp Asp
1385 1390 1395

Ala Asn Phe Pro Arg Ile Glu Ser Ala Ser Met Ser Gly Ala Gly
1400 1405 1410

Arg Lys Thr Ile Tyr Lys Asp Met Lys Thr Gly Ala Trp Pro Asn
1415 1420 1425

Gly Leu Thr Val Asp His Phe Glu Arg Arg Ile Val Trp Thr Asp
1430 1435 1440

Ala Arg Ser Asp Ala Ile Tyr Ser Ala Phe Tyr Asp Gly Thr Asn
1445 1450 1455

Met Ile Glu Ile Ile Arg Gly His Glu Tyr Leu Ser His Pro Phe
1460 1465 1470

Ala Val Ser Leu Tyr Gly Ser Glu Val Tyr Trp Thr Asp Trp Arg
1475 1480 1485

Thr Asn Thr Leu Ala Lys Ala Asn Lys Trp Thr Gly Gln Asn Val
1490 1495 1500

Ser Val Ile Gln Lys Thr Ser Ala Gln Pro Phe Asp Leu Gln Ile
1505 1510 1515

Tyr His Pro Ser Arg Gln Pro Gln Ala Pro Asn Pro Cys Ala Ala
1520 1525 1530

Asn Glu Gly Arg Gly Pro Cys Ser His Leu Cys Leu Ile Asn His
1535 1540 1545

Asn Arg Ser Ala Ala Cys Ala Cys Pro His Leu Met Lys Leu Ser
1550 1555 1560

Ser Asp Lys Lys Thr Cys Tyr Glu Met Lys Lys Phe Leu Leu Tyr
1565 1570 1575

Ala Arg Arg Ser Glu Ile Arg Gly Val Asp Ile Asp Asn Pro Tyr
1580 1585 1590

Val Asn Phe Ile Thr Ala Phe Thr Val Pro Asp Ile Asp Asp Val
1595 1600 1605

Ala Val Ile Asp Phe Asp Ala Ser Glu Glu Arg Leu Tyr Trp Thr
1610 1615 1620

Asp Ile Lys Thr Gln Thr Ile Thr Arg Ala Phe Ile Asn Gly Thr
1625 1630 1635

Gly Leu Glu Thr Val Ile Ser Arg Asp Ile Gln Ser Ile Arg Gly
1640 1645 1650

Leu Ala Val Asp Trp Val Ser Arg Asn Leu Tyr Trp Ile Ser Ser
1655 1660 1665

Glu Phe Asp Glu Thr Gln Ile Asn Val Ala Arg Leu Asp Gly Ser
1670 1675 1680

Leu Lys Thr Ser Ile Ile His Gly Ile Asp Lys Pro Gln Cys Leu
1685 1690 1695

Ala Ala His Pro Val Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asn
1700 1705 1710

Thr Ile Asn Met Ala Asn Met Asp Gly Ser Asn Ser Lys Ile Leu
1715 1720 1725

Phe Gln Asn Gln Lys Glu Pro Val Gly Leu Ser Ile Asp Tyr Val
1730 1735 1740

Glu Asn Lys Leu Tyr Trp Ile Ser Ser Gly Asn Gly Thr Ile Asn
1745 1750 1755

Arg Cys Asn Leu Asp Gly Gly Asn Leu Glu Val Ile Glu Ser Met
1760 1765 1770

Lys Glu Glu Leu Thr Lys Ala Thr Ala Leu Thr Ile Met Asp Lys
1775 1780 1785

Lys Leu Trp Trp Ala Asp Gln Asn Leu Ala Gln Leu Gly Thr Cys
1790 1795 1800

Asn Lys Arg Asp Gly Arg Asn Pro Ser Ile Leu Arg Asn Lys Thr
1805 1810 1815

Ser Gly Val Val His Met Lys Val Tyr Asp Lys Glu Ala Gln Gln
1820 1825 1830

Gly Ser Asn Ser Cys Gln Val Asn Asn Gly Gly Cys Ser Gln Leu
1835 1840 1845

Cys Leu Pro Thr Ser Glu Thr Thr Arg Thr Cys Met Cys Thr Val
1850 1855 1860

Gly Tyr Tyr Leu Gln Lys Asn Arg Met Ser Cys Gln Gly Ile Glu
1865 1870 1875

Ser Phe Leu Met Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro
1880 1885 1890

Leu Glu Pro Arg Asp Lys Val Asp Ala Leu Met Pro Ile Ser Gly
1895 1900 1905

Ala Ala Phe Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr
1910 1915 1920

Ile Tyr Trp Thr Asp Met Gly Leu Asn Lys Ile Ser Arg Ala Lys
1925 1930 1935

Arg Asp Gln Thr Trp Lys Glu Asp Val Val Thr Asn Gly Leu Gly
1940 1945 1950

Arg Val Glu Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr
1955 1960 1965

Trp Thr Asp His Gly Phe Asn Leu Ile Glu Val Ala Arg Leu Asn
1970 1975 1980

Gly Ser Phe Arg Tyr Val Ile Ile Ser Gln Gly Leu Asp Gln Pro
1985 1990 1995

Arg Ser Ile Ala Val His Pro Glu Lys Gly Phe Leu Phe Trp Thr
2000 2005 2010

Glu Trp Gly Gln Val Pro Cys Ile Gly Lys Ala Arg Leu Asp Gly
2015 2020 2025

Ser Glu Lys Val Met Ile Val Ser Val Gly Ile Thr Trp Pro Asn
2030 2035 2040

Gly Ile Ser Ile Asp Tyr Glu Glu Asn Lys Leu Tyr Trp Cys Asp
2045 2050 2055

Ala Arg Ser Asp Lys Ile Glu Arg Ile Asp Leu Asp Thr Gly Ala
2060 2065 2070

Asn Arg Glu Val Leu Leu Ser Gly Ser Asn Val Asp Leu Phe Ser
2075 2080 2085

Val Ala Val Phe Gly Ala Tyr Ile Tyr Trp Ser Asp Arg Ala His
2090 2095 2100

Ala Asn Gly Ser Val Arg Arg Gly His Lys Asn Asp Ala Thr Glu
2105 2110 2115

Thr Val Thr Met Arg Thr Gly Leu Gly Val Asn Leu Lys Glu Ile
2120 2125 2130

Lys Ile Phe Asn Arg Val Arg Glu Lys Gly Thr Asn Val Cys Ala
2135 2140 2145

Lys Glu Asn Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Asn
2150 2155 2160

Ser Arg Arg Thr Cys Ala Cys Ala His Gly Tyr Leu Ala Gly Asp
2165 2170 2175

Gly Val Thr Cys Leu Arg His Glu Gly Tyr Leu Leu Tyr Ser Gly
2180 2185 2190

Arg Thr Ile Leu Lys Ser Ile His Leu Ser Asp Glu Thr Asn Leu
2195 2200 2205

Asn Ser Pro Val Arg Pro Tyr Glu Asn Pro Asn Tyr Phe Lys Asn
2210 2215 2220

Ile Ile Ala Leu Ala Phe Asp Tyr Asn Gln Arg Arg Glu Gly Thr
2225 2230 2235

Asn Arg Ile Phe Tyr Ser Asp Ala His Phe Gly Asn Ile Gln Leu
2240 2245 2250

Ile Lys Asp Asn Trp Glu Asp Arg Gln Val Ile Val Glu Asn Val
2255 2260 2265

Gly Ser Val Glu Gly Leu Ala Tyr His Arg Ala Trp Asp Thr Leu
2270 2275 2280

Tyr Trp Thr Ser Ser Ser Thr Ser Ser Ile Thr Arg His Thr Val
2285 2290 2295

Asp Gln Thr Arg Pro Gly Ala Ile Asp Arg Glu Ala Val Ile Thr
2300 2305 2310

Met Ser Glu Asp Asp His Pro His Val Leu Ala Leu Asp Glu Cys
2315 2320 2325

Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Gln His Pro Ser
2330 2335 2340

Ile Met Arg Ala Thr Leu Thr Gly Lys Asn Ala His Val Val Val
2345 2350 2355

Ser Thr Asp Ile Leu Thr Pro Asn Gly Leu Thr Ile Asp His Arg
2360 2365 2370

Ala Glu Lys Leu Tyr Phe Ser Asp Gly Ser Leu Gly Lys Ile Glu
2375 2380 2385

Arg Cys Glu Tyr Asp Gly Ser Gln Arg His Val Ile Val Lys Ser
2390 2395 2400

Gly Pro Gly Thr Phe Leu Ser Leu Ala Val Tyr Asp Ser Tyr Ile
2405 2410 2415

Phe Trp Ser Asp Trp Gly Arg Arg Ala Ile Leu Arg Ser Asn Lys
2420 2425 2430

Tyr Thr Gly Gly Glu Thr Lys Ile Leu Arg Ser Asp Ile Pro His
2435 2440 2445

Gln Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys
2450 2455 2460

Glu Leu Ser Pro Cys Ala Leu Leu Asn Gly Gly Cys His Asp Leu
2465 2470 2475

Cys Leu Leu Thr Pro Asp Gly Arg Val Asn Cys Ser Cys Arg Gly
2480 2485 2490

Asp Arg Val Leu Leu Ala Asn Asn Arg Cys Val Thr Lys Asn Ser
2495 2500 2505

Ser Cys Asn Ile Tyr Ser Glu Phe Glu Cys Gly Asn Gly Asp Cys
2510 2515 2520

Val Asp Tyr Val Leu Thr Cys Asp Gly Ile Pro His Cys Lys Asp
2525 2530 2535

Lys Ser Asp Glu Lys Leu Leu Tyr Cys Glu Asn Arg Ser Cys Arg
2540 2545 2550

Ser Gly Phe Lys Pro Cys Tyr Asn Arg Arg Cys Val Pro His Gly
2555 2560 2565

Lys Leu Cys Asp Gly Thr Asn Asp Cys Gly Asp Ser Ser Asp Glu
2570 2575 2580

Leu Asp Cys Lys Val Ser Thr Cys Ser Thr Val Glu Phe Arg Cys
2585 2590 2595

Ala Asp Gly Thr Cys Ile Pro Arg Ser Ala Arg Cys Asn Gln Asn
2600 2605 2610

Met Asp Cys Ser Asp Ala Ser Asp Glu Lys Gly Cys Asn Asn Thr
2615 2620 2625

Asp Cys Thr His Phe Tyr Lys Leu Gly Val Lys Ser Thr Gly Phe
2630 2635 2640

Ile Arg Cys Asn Ser Thr Ser Leu Cys Val Leu Pro Ser Trp Ile
2645 2650 2655

Cys Asp Gly Ser Asn Asp Cys Gly Asp Tyr Ser Asp Glu Leu Lys
2660 2665 2670

Cys Pro Val Gln Asn Lys His Lys Cys Glu Glu Asn Tyr Phe Gly
2675 2680 2685

Cys Pro Ser Gly Arg Cys Ile Leu Asn Thr Trp Val Cys Asp Gly
2690 2695 2700

Gln Lys Asp Cys Glu Asp Gly Leu Asp Glu Leu His Cys Asp Ser
2705 2710 2715

Ser Cys Ser Trp Asn Gln Phe Ala Cys Ser Val Lys Lys Cys Ile
2720 2725 2730

Ser Lys His Trp Ile Cys Asp Gly Glu Asp Asp Cys Gly Asp Ser
2735 2740 2745

Leu Asp Glu Ser Asp Ser Ile Cys Gly Ala Val Thr Cys Ala Ala
2750 2755 2760

Asp Met Phe Ser Cys Gln Gly Ser His Ala Cys Val Pro Gln His
2765 2770 2775

Trp Leu Cys Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu
2780 2785 2790

Leu Ser Ser Ala Gly Cys Ala Pro Asn Asn Thr Cys Asp Glu Asn
2795 2800 2805

Ala Phe Met Cys His Asn Lys Val Cys Ile Pro Lys Gln Phe Val
2810 2815 2820

Cys Asp His Asp Asp Asp Cys Gly Asp Gly Ser Asp Glu Phe Leu
2825 2830 2835

Gln Cys Gly Tyr Arg Gln Cys Gly Pro Glu Glu Phe Arg Cys Ala
2840 2845 2850

Asp Gly Arg Cys Leu Val Asn Thr Leu Trp Gln Cys Asp Gly Asp
2855 2860 2865

Phe Asp Cys Pro Asp Ser Ser Asp Glu Ala Pro Ile Asn Pro Arg
2870 2875 2880

Cys Arg Ser Ala Glu His Ser Cys Asn Ser Ser Phe Phe Met Cys
2885 2890 2895

Lys Asn Gly Arg Cys Ile Pro Ser Asp Gly Leu Cys Asp Ile Arg
2900 2905 2910

Asp Asp Cys Gly Asp Gly Ser Asp Glu Thr Asn Cys His Ile Asn
2915 2920 2925

Glu Cys Leu Ser Lys Lys Ile Ser Gly Cys Ser Gln Asp Cys Gln
2930 2935 2940

Asp Leu Pro Val Ser Tyr Lys Cys Lys Cys Trp Pro Gly Phe Gln
2945 2950 2955

Leu Lys Asp Asp Gly Lys Thr Cys Val Asp Ile Asp Glu Cys Ser
2960 2965 2970

Ser Gly Phe Pro Cys Ser Gln Gln Cys Ile Asn Thr Tyr Gly Thr
2975 2980 2985

Tyr Lys Cys His Cys Ala Glu Gly Tyr Glu Thr Gln Pro Asp Asn
2990 2995 3000

Pro Asn Gly Cys Arg Ser Leu Ser Asp Glu Glu Pro Phe Leu Ile
3005 3010 3015

Leu Ala Asp Gln His Glu Ile Arg Lys Ile Ser Thr Asp Gly Ser
3020 3025 3030

Asn Tyr Thr Leu Leu Lys Gln Gly Leu Asn Asn Val Ile Ala Leu
3035 3040 3045

Asp Phe Asp Tyr Arg Glu Glu Phe Ile Tyr Trp Ile Asp Ser Ser
3050 3055 3060

Arg Pro Asn Gly Ser Arg Ile Asn Arg Met Cys Leu Asn Gly Ser
3065 3070 3075

Asp Ile Lys Val Val His Asn Thr Ala Val Pro Asn Ala Leu Ala
3080 3085 3090

Val Asp Trp Ile Gly Lys Asn Leu Tyr Trp Ser Asp Thr Glu Lys
3095 3100 3105

Arg Ile Ile Glu Val Ser Lys Leu Asn Gly Leu Tyr Pro Thr Val
3110 3115 3120

Leu Val Ser Lys Arg Leu Lys Phe Pro Arg Asp Leu Ser Leu Asp
3125 3130 3135

Pro Arg Ala Gly Asn Leu Tyr Trp Ile Asp Cys Cys Glu Tyr Pro
3140 3145 3150

His Ile Gly Arg Val Gly Met Asp Gly Thr Asn Gln Ser Val Val
3155 3160 3165

Ile Glu Thr Lys Ile Ser Arg Pro Met Ala Leu Thr Ile Asp Tyr
3170 3175 3180

Val Asn His Arg Leu Tyr Trp Ala Asp Glu Asn His Ile Glu Phe
3185 3190 3195

Ser Asn Met Asp Gly Ser His Arg His Lys Val Pro Asn Gln Asp
3200 3205 3210

Ile Pro Gly Val Ile Ala Leu Thr Leu Phe Glu Asp Tyr Ile Tyr
3215 3220 3225

Trp Thr Asp Gly Lys Thr Lys Ser Leu Ser Arg Val His Lys Thr
3230 3235 3240

Ser Gly Ala Asp Arg Leu Ser Leu Ile Asn Ser Trp His Ala Ile
3245 3250 3255

Thr Asp Ile Gln Val Tyr His Ser Tyr Arg Gln Pro Asp Val Ser
3260 3265 3270

Lys His Leu Cys Thr Val Asn Asn Gly Gly Cys Ser His Leu Cys
3275 3280 3285

Leu Leu Gly Pro Gly Lys Thr His Thr Cys Ala Cys Pro Thr Asn
3290 3295 3300

Phe Tyr Leu Ala Ala Asp Asn Arg Thr Cys Leu Ser Asn Cys Thr
3305 3310 3315

Ala Ser Gln Phe Arg Cys Lys Thr Asp Lys Cys Ile Pro Phe Trp
3320 3325 3330

Trp Lys Cys Asp Thr Val Asp Asp Cys Gly Asp Gly Ser Asp Glu
3335 3340 3345

Pro Asp Asp Cys Pro Glu Phe Lys Cys Gln Pro Gly Arg Phe Gln
3350 3355 3360

Cys Gly Thr Gly Leu Cys Ala Leu Pro Ala Phe Ile Cys Asp Gly
3365 3370 3375

Glu Asn Asp Cys Gly Asp Asn Ser Asp Glu Leu Asn Cys Asp Thr
3380 3385 3390

His Val Cys Leu Ala Gly Gln Phe Lys Cys Thr Lys Asn Lys Lys
3395 3400 3405

Cys Ile Pro Val Asn Leu Arg Cys Asn Gly Gln Asp Asp Cys Gly
3410 3415 3420

Asp Glu Glu Asp Glu Lys Asp Cys Pro Glu Asn Ser Cys Ser Pro
3425 3430 3435

Asp Tyr Phe Gln Cys Lys Thr Thr Lys His Cys Ile Ser Lys Leu
3440 3445 3450

Trp Val Cys Asp Glu Asp Pro Asp Cys Ala Asp Ala Ser Asp Glu
3455 3460 3465

Ala Asn Cys Asp Lys Lys Thr Cys Gly Pro His Glu Phe Gln Cys
3470 3475 3480

Lys Asn Asn Asn Cys Ile Pro Asp His Trp Arg Cys Asp Asn Gln
3485 3490 3495

Asn Asp Cys Ser Asp Asn Ser Asp Glu Asp Asn Cys Lys Pro Gln
3500 3505 3510

Thr Cys Thr Leu Lys Asp Phe Leu Cys Ser Asn Gly Asp Cys Val
3515 3520 3525

Ser Ser Arg Phe Trp Cys Asp Gly Glu Phe Asp Cys Ala Asp Gly
3530 3535 3540

Ser Asp Glu Lys Asn Cys Glu Thr Ser Cys Ser Lys Asp Gln Phe
3545 3550 3555

Gln Cys Ser Asn Gly Gln Cys Leu Ser Ala Lys Trp Lys Cys Asp
3560 3565 3570

Gly His Glu Asp Cys Lys Tyr Gly Glu Asp Glu Lys Asn Cys Glu
3575 3580 3585

Pro Ala Phe Pro Val Cys Ser Ser Ser Glu Tyr Met Cys Ala Ser
3590 3595 3600

Gly Gly Cys Leu Ser Ala Ser Leu Lys Cys Asn Gly Glu Pro Asp
3605 3610 3615

Cys Val Asp Gly Ser Asp Glu Met Asp Cys Val Ile Glu Cys Lys
3620 3625 3630

Glu Asp Gln Phe Gln Cys Lys Asn Lys Ala Tyr Cys Ile Pro Ile
3635 3640 3645

Arg Trp Leu Cys Asp Gly Ile Tyr Asp Cys Val Asp Gly Ser Asp
3650 3655 3660

Glu Glu Thr Cys Gly Arg Gly Gly Ser Ile Cys Arg Asp Asp Glu
3665 3670 3675

Phe Leu Cys Asn Asn Ser Leu Cys Lys Leu His Phe Trp Val Cys
3680 3685 3690

Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu Ala Pro Asp
3695 3700 3705

Met Cys Val Lys Phe Leu Cys Pro Pro Thr Arg Pro Tyr Arg Cys
3710 3715 3720

Arg Asn Asp Arg Ile Cys Leu Gln Leu Glu Lys Ile Cys Asn Gly
3725 3730 3735

Ile Asn Asp Cys Gly Asp Asn Ser Asp Glu Glu His Cys Ser Gly
3740 3745 3750

Lys Leu Ser Leu Lys Ser Lys Pro Cys Lys Lys Asp Glu Phe Thr
3755 3760 3765

Cys Ser Asn Arg Asn Cys Ile Pro Met Glu Leu Gln Cys Asp Ser
3770 3775 3780

Leu Asp Asp Cys Gly Asp Gly Ser Asp Glu Gln Gly Cys Leu Lys
3785 3790 3795

Thr Pro Ile Glu His Thr Cys Glu Asn Asn Gly Asn Pro Cys Gly
3800 3805 3810

Asp Asp Ala Tyr Cys Asn Gln Ile Lys Thr Ser Val Phe Cys Arg
3815 3820 3825

Cys Lys Pro Gly Phe Gln Arg Asn Met Lys Gly Arg Glu Cys Ala
3830 3835 3840

Asp Leu Asn Glu Cys Leu Leu Phe Gly Ile Cys Ser His His Cys
3845 3850 3855

Leu Asn Thr Arg Gly Ser Tyr Lys Cys Val Cys Asp Gln Asn Phe
3860 3865 3870

Gln Glu Lys Asn Asn Ser Cys Ile Ala Lys Gly Ser Glu Asp Gln
3875 3880 3885

Ala Leu Tyr Ile Ala Asn Asp Thr Asp Ile Leu Gly Phe Val Tyr
3890 3895 3900

Pro Phe Asn Tyr Ser Gly Gly His Gln Gln Ile Ser His Val Glu
3905 3910 3915

His Asn Ser Arg Ile Thr Gly Met Asp Val His Tyr Gln Arg Asn
3920 3925 3930

Val Ile Val Trp Ser Thr Gln Phe Asn Pro Gly Gly Ile Phe Tyr
3935 3940 3945

Lys Met Ile Asp Ala Arg Glu Lys Arg Gln Ala Asn Ser Gly Leu
3950 3955 3960

Ile Cys Pro Glu Phe Lys Arg Pro Arg Asp Ile Ala Val Asp Trp
3965 3970 3975

Val Ala Gly Asn Val Tyr Trp Thr Asp His Ser Arg Met His Trp
3980 3985 3990

Phe Ser Tyr Tyr Thr Thr His Trp Thr Ser Leu Arg Tyr Ser Ile
3995 4000 4005

Asn Val Gly Gln Leu Asn Gly Pro Asn Cys Thr Arg Leu Leu Thr
4010 4015 4020

Asn Met Ala Gly Glu Pro Tyr Ala Ile Ala Val Asn Pro Lys Arg
4025 4030 4035

Gly Met Met Tyr Trp Thr Val Ile Gly Asp His Ser His Ile Glu
4040 4045 4050

Glu Ala Ala Met Asp Gly Thr Leu Arg Arg Val Leu Val Gln Lys
4055 4060 4065

Asn Leu Gln Arg Pro Thr Gly Leu Thr Val Asp His Phe Gly Glu
4070 4075 4080

Arg Ile Tyr Trp Ala Asp Phe Glu Leu Ser Ile Ile Gly Ser Val
4085 4090 4095

Leu Tyr Asp Gly Ser Ser Pro Val Val Ser Val Ser Ser Lys Gln
4100 4105 4110

Gly Leu Leu His Pro His Arg Ile Asp Val Phe Glu Asp Tyr Ile
4115 4120 4125

Tyr Gly Ala Gly Pro Lys Asn Gly Ile Phe Arg Val Gln Lys Phe
4130 4135 4140

Gly His Gly Ser Val Glu Val Leu Ala Leu Gly Val Asp Lys Thr
4145 4150 4155

Lys Ser Ile Leu Val Ser His Arg Tyr Lys Gln Leu Asn Leu Pro
4160 4165 4170

Asn Pro Cys Leu Asp Leu Ser Cys Asp Phe Leu Cys Leu Leu Asn
4175 4180 4185

Pro Ser Gly Ala Thr Cys Ile Cys Pro Glu Gly Lys Tyr Met Met
4190 4195 4200

Asn Gly Thr Cys His Asp Asp Ser Leu Leu Asp Asp Ser Cys Lys
4205 4210 4215

Leu Thr Cys Glu Asn Gly Gly Arg Cys Ile Leu Asn Glu Lys Gly
4220 4225 4230

Asp Leu Arg Cys His Cys Trp Pro Ser Tyr Ser Gly Gly Arg Cys
4235 4240 4245

Glu Val Asn His Cys Ser Asn Tyr Cys Gln Asn Gly Gly Thr Cys
4250 4255 4260

Ile Pro Ser Thr Leu Gly Arg Pro Thr Cys Ile Cys Ala Leu Gly
4265 4270 4275

Phe Thr Gly Pro Asn Cys Gly Lys Ala Val Cys Glu Asp Ser Cys
4280 4285 4290

His Asn Gly Gly Ser Cys Val Val Thr Ala Gly Asn Gln Pro Tyr
4295 4300 4305

Cys His Cys Gln Ala Asp Tyr Thr Gly Asp Arg Cys Gln Tyr Tyr
4310 4315 4320

Val Cys His His Tyr Cys Val Asn Ser Glu Ser Cys Thr Ile Gly
4325 4330 4335

Asn Asp Gly Ser Val Glu Cys Val Cys Pro Thr Arg Tyr Glu Gly
4340 4345 4350

Pro Lys Cys Glu Ile Asp Lys Cys Val Arg Cys His Gly Gly His
4355 4360 4365

Cys Ile Ile Asn Lys Asp Asn Glu Asp Ile Phe Cys Asn Cys Thr
4370 4375 4380

Asn Gly Lys Ile Ala Ser Ser Cys Gln Leu Cys Asp Gly Tyr Cys
4385 4390 4395

Tyr Asn Gly Gly Thr Cys Gln Leu Asp Pro Glu Thr Ser Ile Pro
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Val Cys Val Cys Ser Thr Asn Trp Ser Gly Thr Gln Cys Glu Arg
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Pro Ala Pro Lys Ser Ser Lys Ser Glu His Ile Ser Thr Arg Ser
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Ile Ala Ile Ile Val Pro Leu Val Leu Leu Val Thr Leu Val Thr
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Thr Leu Val Ile Gly Leu Val Val Cys Lys Arg Lys Arg Arg Thr
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Lys Thr Ile Arg Arg Gln Pro Ile Ile Asn Gly Gly Ile Asn Val
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Glu Ile Gly Asn Pro Ser Tyr Asn Met Tyr Glu Val Asp His Asp
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His Ser Asp Gly Gly Leu Leu Glu Pro Ser Phe Met Ile Asp Pro
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Val Lys Ser Arg Tyr Ile Gly Gly Gly Ser Ser Ala Phe Lys Leu
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Pro His Thr Ala Pro Pro Ile Tyr Leu Asn Ser Asp Leu Lys Gly
4535 4540 4545

Pro Leu Thr Phe Gly Pro Thr Asn Tyr Ser Asn Pro Val Tyr Ala
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Lys Leu Tyr Met Asp Gly Gln Asn Cys Arg Asn Ser Leu Ala Ser
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Val Asp Glu Arg Lys Glu Leu Leu Pro Lys Lys Ile Glu Ile Gly
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Ile Arg Glu Thr Val Ala
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<212> PRT

<213> MOUSE

<400> 71

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Phe Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys
35 40 45

Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu Ala Pro Glu Ile
50 55 60

Cys Pro Gln Ser Lys Ala Gln Arg Cys Pro Pro Asn Glu His Ser Cys
65 70 75 80

Leu Gly Thr Glu Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Ile
85 90 95

Gln Asp Cys Met Asp Gly Ser Asp Glu Gly Ala His Cys Arg Glu Leu
100 105 110

Arg Ala Asn Cys Ser Arg Met Gly Cys Gln His His Cys Val Pro Thr
115 120 125

Pro Ser Gly Pro Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Gln Ala
130 135 140

Asp Gly Lys Thr Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr
145 150 155 160

Cys Ser Gln Leu Cys Thr Asn Thr Asp Gly Ser Phe Thr Cys Gly Cys
165 170 175

Val Glu Gly Tyr Leu Leu Gln Pro Asp Asn Arg Ser Cys Lys Ala Lys
180 185 190

Asn Glu Pro Val Asp Arg Pro Pro Val Leu Leu Ile Ala Asn Ser Gln
195 200 205

Asn Ile Leu Ala Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr
210 215 220

Pro Thr Ser Thr Arg Gln Thr Thr Ala Met Asp Phe Ser Tyr Ala Asn
225 230 235 240

Glu Thr Val Cys Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln
245 250 255

Leu Lys Cys Ala Arg Met Pro Gly Leu Lys Gly Phe Val Asp Glu His
260 265 270

Thr Ile Asn Ile Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile
275 280 285

Asp Trp Leu Thr Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg
290 295 300

Ile Phe Val Cys Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp
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Leu Glu Leu Tyr Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly
325 330 335

Lys Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys
340 345 350

Asp Met Asp Gly Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val
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Phe Pro His Gly Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp
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Ala Asp Ala Tyr Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys
385 390 395 400

Gly Arg Gln Thr Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly
405 410 415

Leu Thr Val Phe Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala
420 425 430

Asn Thr Gln Gln Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser
435 440 445

Thr Glu Tyr Gln Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His
450 455 460

Ile Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu
465 470 475 480

Asn Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu
485 490 495

Ala Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser
500 505 510

Leu Gly Ser Asp Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe
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Leu Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met
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Gly Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met
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Asn Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe
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Ala Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr
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Glu Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val
595 600 605

Ala Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro
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Lys Lys Thr Ile Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg
625 630 635 640

Lys Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val
645 650 655

Asp Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro
660 665 670

Lys Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser
675 680 685

His Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly
690 695 700

Leu Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe
705 710 715 720

Tyr Asp Arg Ile Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile
725 730 735

Val Tyr Glu Gly Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His
740 745 750

Gly Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg
755 760 765

Leu Glu Arg Gly Val Ala Gly Ala Pro Pro Thr Val Thr Leu Leu Arg
770 775 780

Ser Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln
785 790 795 800

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Gln Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser
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Ser Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu
            820                 825                 830

Asp Gln Val Leu Asp Thr Asp Gly Val Thr Cys Leu Ala Asn Pro Ser
        835                 840                 845

Tyr Val Pro Pro Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn
    850                 855                 860

Asn Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys
865                 870                 875                 880

Leu Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys
                885                 890                 895

Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg
            900                 905                 910

Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser
        915                 920                 925

Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys
    930                 935                 940

Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp
945                 950                 955                 960

Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr
                965                 970                 975

Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn
            980                 985                 990

Ile Asn Trp Arg Cys Asp Asn Asp  Asn Asp Cys Gly Asp  Asn Ser Asp
        995                 1000                1005

Glu Ala  Gly Cys Ser His Ser  Cys Ser Ser Thr Gln  Phe Lys Cys
    1010                1015                1020

Asn Ser  Gly Arg Cys Ile Pro  Glu His Trp Thr Cys  Asp Gly Asp
    1025                1030                1035

Asn Asp  Cys Gly Asp Tyr Ser  Asp Glu Thr His Ala  Asn Cys Thr
    1040                1045                1050

Asn Gln  Ala Thr Arg Pro Pro  Gly Gly Cys His Ser  Asp Glu Phe
    1055                1060                1065
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Gln Cys Arg Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys
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Asp Gly Asp Thr Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys
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Glu Gly Val Thr His Val Cys Asp Pro Asn Val Lys Phe Gly Cys
1100 1105 1110

Lys Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val Cys Asp Gly
1115 1120 1125

Asp Ser Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys Glu Ala
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Leu Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser
1145 1150 1155

Val Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Lys Asp Asp Cys
1160 1165 1170

Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp Gln Cys Ser Leu
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Asn Asn Gly Gly Cys Ser His Asn Cys Ser Val Ala Pro Gly Glu
1190 1195 1200

Gly Ile Val Cys Ser Cys Pro Leu Gly Met Glu Leu Gly Ser Asp
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Asn His Thr Cys Gln Ile Gln Ser Tyr Cys Ala Lys His Leu Lys
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Cys Ser Gln Lys Cys Asp Gln Asn Lys Phe Ser Val Lys Cys Ser
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Cys Tyr Glu Gly Trp Val Leu Glu Pro Asp Gly Glu Ser Cys Arg
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Ser Leu Asp Pro Phe Lys Pro Phe Ile Ile Phe Ser Asn Arg His
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Glu Ile Arg Arg Ile Asp Leu His Lys Gly Asp Tyr Ser Val Leu
1280 1285 1290

Val Pro Gly Leu Arg Asn Thr Ile Ala Leu Asp Phe His Leu Ser
1295 1300 1305

Gln Ser Ala Leu Tyr Trp Thr Asp Val Val Glu Asp Lys Ile Tyr
1310 1315 1320

Arg Gly Lys Leu Leu Asp Asn Gly Ala Leu Thr Ser Phe Glu Val
1325 1330 1335

Val Ile Gln Tyr Gly Leu Ala Thr Pro Glu Gly Leu Ala Val Asp
1340 1345 1350

Trp Ile Ala Gly Asn Ile Tyr Trp Val Glu Ser Asn Leu Asp Gln
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Ile Glu Val Ala Lys Leu Asp Gly Thr Leu Arg Thr Thr Leu Leu
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Ala Gly Asp Ile Glu His Pro Arg Ala Ile Ala Leu Asp Pro Arg
1385 1390 1395

Asp Gly Ile Leu Phe Trp Thr Asp Trp Asp Ala Ser Leu Pro Arg
1400 1405 1410

Ile Glu Ala Ala Ser Met Ser Gly Ala Gly Arg Arg Thr Ile His
1415 1420 1425

Arg Glu Thr Gly Ser Gly Gly Trp Pro Asn Gly Leu Thr Val Asp
1430 1435 1440

Tyr Leu Glu Lys Arg Ile Leu Trp Ile Asp Ala Arg Ser Asp Ala
1445 1450 1455

Ile Tyr Ser Ala Arg Tyr Asp Gly Ser Gly His Met Glu Val Leu
1460 1465 1470

Arg Gly His Glu Phe Leu Ser His Pro Phe Ala Val Thr Leu Tyr
1475 1480 1485

Gly Gly Glu Val Tyr Trp Thr Asp Trp Arg Thr Asn Thr Leu Ala
1490 1495 1500

Lys Ala Asn Lys Trp Thr Gly His Asn Val Thr Val Val Gln Arg
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Thr Asn Thr Gln Pro Phe Asp Leu Gln Val Tyr His Pro Ser Arg
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Gln Pro Met Ala Pro Asn Pro Cys Glu Ala Asn Gly Gly Arg Gly
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Pro Cys Ser His Leu Cys Leu Ile Asn Tyr Asn Arg Thr Val Ser
1550 1555 1560

Cys Ala Cys Pro His Leu Met Lys Leu His Lys Asp Asn Thr Thr
1565 1570 1575

Cys Tyr Glu Phe Lys Lys Phe Leu Leu Tyr Ala Arg Gln Met Glu
1580 1585 1590

Ile Arg Gly Val Asp Leu Asp Ala Pro Tyr Tyr Asn Tyr Ile Ile
1595 1600 1605

Ser Phe Thr Val Pro Asp Ile Asp Asn Val Thr Val Leu Asp Tyr
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Asp Ala Arg Glu Gln Arg Val Tyr Trp Ser Asp Val Arg Thr Gln
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Ala Ile Lys Arg Ala Phe Ile Asn Gly Thr Gly Val Glu Thr Val
1640 1645 1650

Val Ser Ala Asp Leu Pro Asn Ala His Gly Leu Ala Val Asp Trp
1655 1660 1665

Val Ser Arg Asn Leu Phe Trp Thr Ser Tyr Asp Thr Asn Lys Lys
1670 1675 1680

Gln Ile Asn Val Ala Arg Leu Asp Gly Ser Phe Lys Asn Ala Val
1685 1690 1695

Val Gln Gly Leu Glu Gln Pro His Gly Leu Val Val His Pro Leu
1700 1705 1710

Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asp Asn Ile Ser Met Ala
1715 1720 1725

Asn Met Asp Gly Ser Asn His Thr Leu Leu Phe Ser Gly Gln Lys
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Gly Pro Val Gly Leu Ala Ile Asp Phe Pro Glu Ser Lys Leu Tyr
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Trp Ile Ser Ser Gly Asn His Thr Ile Asn Arg Cys Asn Leu Asp
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Gly Ser Glu Leu Glu Val Ile Asp Thr Met Arg Ser Gln Leu Gly
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Lys Ala Thr Ala Leu Ala Ile Met Gly Asp Lys Leu Trp Trp Ala
1790 1795 1800

Asp Gln Val Ser Glu Lys Met Gly Thr Cys Asn Lys Ala Asp Gly
1805 1810 1815

Ser Gly Ser Val Val Leu Arg Asn Ser Thr Thr Leu Val Met His
1820 1825 1830

Met Lys Val Tyr Asp Glu Ser Ile Gln Leu Glu His Glu Gly Thr
1835 1840 1845

Asn Pro Cys Ser Val Asn Asn Gly Asp Cys Ser Gln Leu Cys Leu
1850 1855 1860

Pro Thr Ser Glu Thr Thr Arg Ser Cys Met Cys Thr Ala Gly Tyr
1865 1870 1875

Ser Leu Arg Ser Gly Gln Gln Ala Cys Glu Gly Val Gly Ser Phe
1880 1885 1890

Leu Leu Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro Leu Asp
1895 1900 1905

Pro Asn Asp Lys Ser Asp Ala Leu Val Pro Val Ser Gly Thr Ser
1910 1915 1920

Leu Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr Ile Tyr
1925 1930 1935

Trp Val Asp Met Gly Leu Ser Thr Ile Ser Arg Ala Lys Arg Asp
1940 1945 1950

Gln Thr Trp Arg Glu Asp Val Val Thr Asn Gly Ile Gly Arg Val
1955 1960 1965

Glu Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Thr
1970 1975 1980

Asp Gln Gly Phe Asp Val Ile Glu Val Ala Arg Leu Asn Gly Ser
1985 1990 1995

Phe Arg Tyr Val Val Ile Ser Gln Gly Leu Asp Lys Pro Arg Ala
2000 2005 2010

Ile Thr Val His Pro Glu Lys Gly Tyr Leu Phe Trp Thr Glu Trp
2015 2020 2025

Gly His Tyr Pro Arg Ile Glu Arg Ser Arg Leu Asp Gly Thr Glu
2030 2035 2040

Arg Val Val Leu Val Asn Val Ser Ile Ser Trp Pro Asn Gly Ile
2045 2050 2055

Ser Val Asp Tyr Gln Gly Gly Lys Leu Tyr Trp Cys Asp Ala Arg
2060 2065 2070

Met Asp Lys Ile Glu Arg Ile Asp Leu Glu Thr Gly Glu Asn Arg
2075 2080 2085

Glu Val Val Leu Ser Ser Asn Asn Met Asp Met Phe Ser Val Ser
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Val Phe Glu Asp Phe Ile Tyr Trp Ser Asp Arg Thr His Ala Asn
2105 2110 2115

Gly Ser Ile Lys Arg Gly Cys Lys Asp Asn Ala Thr Asp Ser Val
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Pro Leu Arg Thr Gly Ile Gly Val Gln Leu Lys Asp Ile Lys Val
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Phe Asn Arg Asp Arg Gln Lys Gly Thr Asn Val Cys Ala Val Ala
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Asn Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Gly Gly Gln
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Arg Ala Cys Ala Cys Ala His Gly Met Leu Ala Glu Asp Gly Ala
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Ser Cys Arg Glu Tyr Ala Gly Tyr Leu Leu Tyr Ser Glu Arg Thr
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Ile Leu Lys Ser Ile His Leu Ser Asp Glu Arg Asn Leu Asn Ala
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Pro Val Gln Pro Phe Glu Asp Pro Glu His Met Lys Asn Val Ile
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Ile Asn Asp Asp Gly Ser Gly Arg Thr Thr Ile Val Glu Asn Val
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Gly Ser Val Glu Gly Leu Ala Tyr His Arg Gly Trp Asp Thr Leu
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Tyr Trp Thr Ser Tyr Thr Thr Ser Thr Ile Thr Arg His Thr Val
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Asp Gln Thr Arg Pro Gly Ala Phe Glu Arg Glu Thr Val Ile Thr
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Met Ser Gly Asp Asp His Pro Arg Ala Phe Val Leu Asp Glu Cys
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Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Leu His Pro Ser
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Ile Met Arg Ala Ala Leu Ser Gly Ala Asn Val Leu Thr Leu Ile
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Glu Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala Ile Asp His Arg
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Ala Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp Lys Ile Glu
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Arg Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu Lys Ser
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Glu Pro Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His Ile
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Phe Trp Thr Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys
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Tyr Val Gly Ser Asp Met Lys Leu Leu Arg Val Asp Ile Pro Gln
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Gln Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys
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Glu Leu Ser Pro Cys Arg Ile Asn Asn Gly Gly Cys Gln Asp Leu
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Cys Leu Leu Thr His Gln Gly His Val Asn Cys Ser Cys Arg Gly
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Ser Cys Arg Ala Gln Asp Glu Phe Glu Cys Ala Asn Gly Glu Cys
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Cys Pro Ser Gly Arg Cys Ile Pro Met Ser Trp Thr Cys Asp Lys
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Glu Asp Asp Cys Glu Asn Gly Glu Asp Glu Thr His Cys Asn Lys
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Phe Cys Ser Glu Ala Gln Phe Glu Cys Gln Asn His Arg Cys Ile
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Ser Lys Gln Trp Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly
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Ser Asp Glu Ala Ala His Cys Glu Gly Lys Thr Cys Gly Pro Ser
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Ser Phe Ser Cys Pro Gly Thr His Val Cys Val Pro Glu Arg Trp
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Leu Cys Asp Gly Asp Lys Asp Cys Thr Asp Gly Ala Asp Glu Ser
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Val Thr Ala Gly Cys Leu Tyr Asn Ser Thr Cys Asp Asp Arg Glu
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Tyr Lys Cys Leu Cys Val Glu Gly Tyr Ala Pro Arg Gly Gly Asp
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Pro His Ser Cys Lys Ala Val Thr Asp Glu Glu Pro Phe Leu Ile
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Phe Ala Asn Arg Tyr Tyr Leu Arg Lys Leu Asn Leu Asp Gly Ser
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Tyr Val Thr Glu Arg Ile Tyr Trp Ala Asp Ala Arg Glu Asp Tyr
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Tyr Val Tyr Trp Thr Asp Trp Glu Thr Lys Ser Ile Asn Arg Ala
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His Lys Thr Thr Gly Ala Asn Lys Thr Leu Leu Ile Ser Thr Leu
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His Arg Pro Met Asp Leu His Val Phe His Ala Leu Arg Gln Pro
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Asp Val Pro Asn His Pro Cys Lys Val Asn Asn Gly Gly Cys Ser
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Pro Thr Asn Phe Tyr Leu Gly Gly Asp Gly Arg Thr Cys Val Ser
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Asn Cys Thr Ala Ser Gln Phe Val Cys Lys Asn Asp Lys Cys Ile
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Pro Phe Trp Trp Lys Cys Asp Thr Glu Asp Asp Cys Gly Asp His
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Ser Asp Glu Pro Pro Asp Cys Pro Glu Phe Lys Cys Arg Pro Gly
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Asn Thr Leu Cys Lys Pro Leu Ala Trp Lys Cys Asp Gly Glu Asp
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Asp Cys Gly Asp Asn Ser Asp Glu Asn Pro Glu Glu Cys Ala Arg
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Ala Asp Asp Asn Glu Ile Arg Ser Leu Phe Pro Gly His Pro His
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Ser Ala Tyr Glu Gln Thr Phe Gln Gly Asp Glu Ser Val Arg Ile
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Asp Ala Met Asp Val His Val Lys Ala Gly Arg Val Tyr Trp Thr
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Asn Trp His Thr Gly Thr Ile Ser Tyr Arg Ser Leu Pro Pro Ala
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Ala Pro Pro Thr Thr Ser Asn Arg His Arg Arg Gln Ile Asp Arg
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Gly Val Thr His Leu Asn Ile Ser Gly Leu Lys Met Pro Arg Gly
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Ile Ala Ile Asp Trp Val Ala Gly Asn Val Tyr Trp Thr Asp Ser
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Gly Arg Asp Val Ile Glu Val Ala Gln Met Lys Gly Glu Asn Arg
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Lys Thr Leu Ile Ser Gly Met Ile Asp Glu Pro His Ala Ile Val
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Val Asp Pro Leu Arg Gly Thr Met Tyr Trp Ser Asp Trp Gly Asn
4010 4015 4020

His Pro Lys Ile Glu Thr Ala Ala Met Asp Gly Thr Leu Arg Glu
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Thr Leu Val Gln Asp Asn Ile Gln Trp Pro Thr Gly Leu Ala Val
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Asp Tyr His Asn Glu Arg Leu Tyr Trp Ala Asp Ala Lys Leu Ser
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Val Ile Gly Ser Ile Arg Leu Asn Gly Thr Asp Pro Ile Val Ala
4070 4075 4080

Ala Asp Ser Lys Arg Gly Leu Ser His Pro Phe Ser Ile Asp Val
4085 4090 4095

Phe Glu Asp Tyr Ile Tyr Gly Val Thr Tyr Ile Asn Asn Arg Val
4100 4105 4110

Phe Lys Ile His Lys Phe Gly His Ser Pro Leu Ile Asn Leu Thr
4115 4120 4125

Gly Gly Leu Ser His Ala Ser Asp Val Val Leu Tyr His Gln His
4130 4135 4140

Lys Gln Pro Glu Val Thr Asn Pro Cys Asp Arg Lys Lys Cys Glu
4145 4150 4155

Trp Leu Cys Leu Leu Ser Pro Ser Gly Pro Val Cys Thr Cys Pro
4160 4165 4170

Asn Gly Lys Arg Leu Asp Asn Gly Thr Cys Val Pro Val Pro Ser
4175 4180 4185

Pro Thr Pro Pro Pro Asp Ala Pro Arg Pro Gly Thr Cys Thr Leu
4190 4195 4200

Gln Cys Phe Asn Gly Gly Ser Cys Phe Leu Asn Ala Arg Arg Gln
4205 4210 4215

Pro Lys Cys Arg Cys Gln Pro Arg Tyr Thr Gly Asp Lys Cys Glu
4220 4225 4230

Leu Asp Gln Cys Trp Glu Tyr Cys His Asn Gly Gly Thr Cys Ala
4235 4240 4245

Ala Ser Pro Ser Gly Met Pro Thr Cys Arg Cys Pro Thr Gly Phe
4250 4255 4260

Thr Gly Pro Lys Cys Thr Ala Gln Val Cys Ala Gly Tyr Cys Ser
4265 4270 4275

Asn Asn Ser Thr Cys Thr Val Asn Gln Gly Asn Gln Pro Gln Cys
4280 4285 4290

Arg Cys Leu Pro Gly Phe Leu Gly Asp Arg Cys Gln Tyr Arg Gln
4295 4300 4305

Cys Ser Gly Phe Cys Glu Asn Phe Gly Thr Cys Gln Met Ala Ala
4310 4315 4320

Asp Gly Ser Arg Gln Cys Arg Cys Thr Val Tyr Phe Glu Gly Pro
4325 4330 4335

Arg Cys Glu Val Asn Lys Cys Ser Arg Cys Leu Gln Gly Ala Cys
4340 4345 4350

Val Val Asn Lys Gln Thr Gly Asp Val Thr Cys Asn Cys Thr Asp
4355 4360 4365

Gly Arg Val Ala Pro Ser Cys Leu Thr Cys Ile Asp His Cys Ser
4370 4375 4380

Asn Gly Gly Ser Cys Thr Met Asn Ser Lys Met Met Pro Glu Cys
4385 4390 4395

Gln Cys Pro Pro His Met Thr Gly Pro Arg Cys Glu Glu Gln Val
4400 4405 4410

Val Ser Gln Gln Gln Pro Gly His Met Ala Ser Ile Leu Ile Pro
4415 4420 4425

Leu Leu Leu Leu Leu Leu Leu Leu Leu Val Ala Gly Val Val Phe
4430 4435 4440

Trp Tyr Lys Arg Arg Val Arg Gly Ala Lys Gly Phe Gln His Gln
4445 4450 4455

Arg Met Thr Asn Gly Ala Met Asn Val Glu Ile Gly Asn Pro Thr
4460 4465 4470

Tyr Lys Met Tyr Glu Gly Gly Glu Pro Asp Asp Val Gly Gly Leu
4475 4480 4485

Leu Asp Ala Asp Phe Ala Leu Asp Pro Asp Lys Pro Thr Asn Phe
4490 4495 4500

Thr Asn Pro Val Tyr Ala Thr Leu Tyr Met Gly Gly His Gly Ser
4505 4510 4515

Arg His Ser Leu Ala Ser Thr Asp Glu Lys Arg Glu Leu Leu Gly
4520 4525 4530

Arg Gly Pro Glu Asp Glu Ile Gly Asp Pro Leu Ala
4535 4540 4545

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Arg Ser Gly Ala Asp Val Asn Met Asp Ile Gly Val Ser Pro Phe Gly
20 25 30

Pro Glu Thr Ile Ile Asp Arg Ser Met Ala Met Asn Glu Gln Phe Val
35 40 45

Met Glu Val Gly Lys Gln Pro Val Ile Phe Glu Asn Pro Met Tyr Ala
50 55 60

Ala Lys Asp Ser Thr Ser Lys Val Gly Leu Ala Val Gln Gly Pro Ser

65 70 75 80

Val Ser Ser Gln Val Thr Val Pro Glu Asn Val Glu Asn Gln Asn Tyr
85 90 95

Gly Arg Ser Ile Asp Pro Ser Glu Ile Val Pro Glu Pro Lys Pro Ala
100 105 110

Ser Pro Gly Ala Asp Glu Thr Gln Gly Thr Lys Trp Asn Ile Phe Lys
115 120 125

Arg Lys Pro Lys Gln Thr Thr Asn Phe Glu Asn Pro Ile Tyr Ala Glu
130 135 140

Met Asp Thr Glu Gln Lys Glu Ala Val Ala Val Ala Pro Pro Pro Ser
145 150 155 160

Pro Ser Leu Pro Ala Lys Ala Ser Lys Arg Ser Ser Thr Pro Gly Tyr
165 170 175

Thr Ala Thr Glu Asp Thr Phe Lys Asp Thr Ala Asn Leu Val Lys Glu
180 185 190

Asp Ser Asp Val
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<210> 73
<211> 2867
<212> PRT
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<400> 73

Met Asp Arg Gly Pro Ala Ala Val Ala Cys Thr Leu Leu Leu Ala Leu
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Val Ala Cys Leu Ala Pro Ala Ser Gly Gln Glu Cys Asp Ser Ala His
20 25 30

Phe Arg Cys Gly Ser Gly His Cys Ile Pro Ala Asp Trp Arg Cys Asp
35 40 45

Gly Thr Lys Asp Cys Ser Asp Asp Ala Asp Glu Ile Gly Cys Ala Val
50 55 60

Val Thr Cys Gln Gln Gly Tyr Phe Lys Cys Gln Ser Glu Gly Gln Cys
65 70 75 80

Ile Pro Asn Ser Trp Val Cys Asp Gln Asp Gln Asp Cys Asp Asp Gly
85 90 95

Ser Asp Glu Arg Gln Asp Cys Ser Gln Ser Thr Cys Ser Ser His Gln
100 105 110

Ile Thr Cys Ser Asn Gly Gln Cys Ile Pro Ser Glu Tyr Arg Cys Asp
115 120 125

His Val Arg Asp Cys Pro Asp Gly Ala Asp Glu Asn Asp Cys Gln Tyr
130 135 140

Pro Thr Cys Glu Gln Leu Thr Cys Asp Asn Gly Ala Cys Tyr Asn Thr
145 150 155 160

Ser Gln Lys Cys Asp Trp Lys Val Asp Cys Arg Asp Ser Ser Asp Glu
165 170 175

Ile Asn Cys Thr Glu Ile Cys Leu His Asn Glu Phe Ser Cys Gly Asn
180 185 190

Gly Glu Cys Ile Pro Arg Ala Tyr Val Cys Asp His Asp Asn Asp Cys
195 200 205

Gln Asp Gly Ser Asp Glu His Ala Cys Asn Tyr Pro Thr Cys Gly Gly
210 215 220

Tyr Gln Phe Thr Cys Pro Ser Gly Arg Cys Ile Tyr Gln Asn Trp Val
225 230 235 240

Cys Asp Gly Glu Asp Asp Cys Lys Asp Asn Gly Asp Glu Asp Gly Cys
245 250 255

Glu Ser Gly Pro His Asp Val His Lys Cys Ser Pro Arg Glu Trp Ser
260 265 270

Cys Pro Glu Ser Gly Arg Cys Ile Ser Ile Tyr Lys Val Cys Asp Gly
275 280 285

Ile Leu Asp Cys Pro Gly Arg Glu Asp Glu Asn Asn Thr Ser Thr Gly
290 295 300

Lys Tyr Cys Ser Met Thr Leu Cys Ser Ala Leu Asn Cys Gln Tyr Gln
305 310 315 320

Cys His Glu Thr Pro Tyr Gly Gly Ala Cys Phe Cys Pro Pro Gly Tyr
325 330 335

Ile Ile Asn His Asn Asp Ser Arg Thr Cys Val Glu Phe Asp Asp Cys
340 345 350

Gln Ile Trp Gly Ile Cys Asp Gln Lys Cys Glu Ser Arg Pro Gly Arg
355 360 365

His Leu Cys His Cys Glu Glu Gly Tyr Ile Leu Glu Arg Gly Gln Tyr
370 375 380

Cys Lys Ala Asn Asp Ser Phe Gly Glu Ala Ser Ile Ile Phe Ser Asn
385 390 395 400

Gly Arg Asp Leu Leu Ile Gly Asp Ile His Gly Arg Ser Phe Arg Ile
405 410 415

Leu Val Glu Ser Gln Asn Arg Gly Val Ala Val Gly Val Ala Phe His
420 425 430

Tyr His Leu Gln Arg Val Phe Trp Thr Asp Thr Val Gln Asn Lys Val
435 440 445

Phe Ser Val Asp Ile Asn Gly Leu Asn Ile Gln Glu Val Leu Asn Val
450 455 460

Ser Val Glu Thr Pro Glu Asn Leu Ala Val Asp Trp Val Asn Asn Lys
465 470 475 480

Ile Tyr Leu Val Glu Thr Lys Val Asn Arg Ile Asp Met Val Asn Leu
485 490 495

Asp Gly Ser Tyr Arg Val Thr Leu Ile Thr Glu Asn Leu Gly His Pro
500 505 510

Arg Gly Ile Ala Val Asp Pro Thr Val Gly Tyr Leu Phe Phe Ser Asp
515 520 525

Trp Glu Ser Leu Ser Gly Glu Pro Lys Leu Glu Arg Ala Phe Met Asp
530 535 540

Gly Ser Asn Arg Lys Asp Leu Val Lys Thr Lys Leu Gly Trp Pro Ala
545 550 555 560

Gly Val Thr Leu Asp Met Ile Ser Lys Arg Val Tyr Trp Val Asp Ser
565 570 575

Arg Phe Asp Tyr Ile Glu Thr Val Thr Tyr Asp Gly Ile Gln Arg Lys
580 585 590

Thr Val Val His Gly Gly Ser Leu Ile Pro His Pro Phe Gly Val Ser
595 600 605

Leu Phe Glu Gly Gln Val Phe Phe Thr Asp Trp Thr Lys Met Ala Val
610 615 620

Leu Lys Ala Asn Lys Phe Thr Glu Thr Asn Pro Gln Val Tyr Tyr Gln
625 630 635 640

Ala Ser Leu Arg Pro Tyr Gly Val Thr Val Tyr His Ser Leu Arg Gln
645 650 655

Pro Tyr Ala Thr Asn Pro Cys Lys Asp Asn Asn Gly Gly Cys Glu Gln
660 665 670

Val Cys Val Leu Ser His Arg Thr Asp Asn Asp Gly Leu Gly Phe Arg
675 680 685

Cys Lys Cys Thr Phe Gly Phe Gln Leu Asp Thr Asp Glu Arg His Cys
690 695 700

Ile Ala Val Gln Asn Phe Leu Ile Phe Ser Ser Gln Val Ala Ile Arg
705 710 715 720

Gly Ile Pro Phe Thr Leu Ser Thr Gln Glu Asp Val Met Val Pro Val
725 730 735

Ser Gly Asn Pro Ser Phe Phe Val Gly Ile Asp Phe Asp Ala Gln Asp
740 745 750

Ser Thr Ile Phe Phe Ser Asp Met Ser Lys His Met Ile Phe Lys Gln
755 760 765

Lys Ile Asp Gly Thr Gly Arg Glu Ile Leu Ala Ala Asn Arg Val Glu
770 775 780

Asn Val Glu Ser Leu Ala Phe Asp Trp Ile Ser Lys Asn Leu Tyr Trp
785 790 795 800

Thr Asp Ser His Tyr Lys Ser Ile Ser Val Met Arg Leu Ala Asp Lys
805 810 815

Thr Arg Arg Thr Val Val Gln Tyr Leu Asn Asn Pro Arg Ser Val Val
820 825 830

Val His Pro Phe Ala Gly Tyr Leu Phe Phe Thr Asp Trp Phe Arg Pro
835 840 845

Ala Lys Ile Met Arg Ala Trp Ser Asp Gly Ser His Leu Leu Pro Val
850 855 860

Ile Asn Thr Thr Leu Gly Trp Pro Asn Gly Leu Ala Ile Asp Trp Ala
865 870 875 880

Ala Ser Arg Leu Tyr Trp Val Asp Ala Tyr Phe Asp Lys Ile Glu His
885 890 895

Ser Thr Phe Asp Gly Leu Asp Arg Arg Arg Leu Gly His Ile Glu Gln
900 905 910

Met Thr His Pro Phe Gly Leu Ala Ile Phe Gly Glu His Leu Phe Phe
915 920 925

Thr Asp Trp Arg Leu Gly Ala Ile Ile Arg Val Arg Lys Ala Asp Gly
930 935 940

Gly Glu Met Thr Val Ile Arg Ser Gly Ile Ala Tyr Ile Leu His Leu
945 950 955 960

Lys Ser Tyr Asp Val Asn Ile Gln Thr Gly Ser Asn Ala Cys Asn Gln
965 970 975

Pro Thr His Pro Asn Gly Asp Cys Ser His Phe Cys Phe Pro Val Pro
980 985 990

Asn Phe Gln Arg Val Cys Gly Cys Pro Tyr Gly Met Arg Leu Ala Ser
995 1000 1005

Asn His Leu Thr Cys Glu Gly Asp Pro Thr Asn Glu Pro Pro Thr
1010 1015 1020

Glu Gln Cys Gly Leu Phe Ser Phe Pro Cys Lys Asn Gly Arg Cys
1025 1030 1035

Val Pro Asn Tyr Tyr Leu Cys Asp Gly Val Asp Asp Cys His Asp
1040 1045 1050

Asn Ser Asp Glu Gln Leu Cys Gly Thr Leu Asn Asn Thr Cys Ser
1055 1060 1065

Ser Ser Ala Phe Thr Cys Gly His Gly Glu Cys Ile Pro Ala His
1070 1075 1080

Trp Arg Cys Asp Lys Arg Asn Asp Cys Val Asp Gly Ser Asp Glu
1085 1090 1095

His Asn Cys Pro Thr His Ala Pro Ala Ser Cys Leu Asp Thr Gln
1100 1105 1110

Tyr Thr Cys Asp Asn His Gln Cys Ile Ser Lys Asn Trp Val Cys
1115 1120 1125

Asp Thr Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu Lys Asn Cys
1130 1135 1140

Asn Ser Thr Glu Thr Cys Gln Pro Ser Gln Phe Asn Cys Pro Asn
1145 1150 1155

His Arg Cys Ile Asp Leu Ser Phe Val Cys Asp Gly Asp Lys Asp
1160 1165 1170

Cys Val Asp Gly Ser Asp Glu Val Gly Cys Val Leu Asn Cys Thr
1175 1180 1185

Ala Ser Gln Phe Lys Cys Ala Ser Gly Asp Lys Cys Ile Gly Val
1190 1195 1200

Thr Asn Arg Cys Asp Gly Val Phe Asp Cys Ser Asp Asn Ser Asp
1205 1210 1215

Glu Ala Gly Cys Pro Thr Arg Pro Pro Gly Met Cys His Ser Asp
1220 1225 1230

Glu Phe Gln Cys Gln Glu Asp Gly Ile Cys Ile Pro Asn Phe Trp
1235 1240 1245

Glu Cys Asp Gly His Pro Asp Cys Leu Tyr Gly Ser Asp Glu His
1250 1255 1260

Asn Ala Cys Val Pro Lys Thr Cys Pro Ser Ser Tyr Phe His Cys
1265 1270 1275

Asp Asn Gly Asn Cys Ile His Arg Ala Trp Leu Cys Asp Arg Asp
1280 1285 1290

Asn Asp Cys Gly Asp Met Ser Asp Glu Lys Asp Cys Pro Thr Gln
1295 1300 1305

Pro Phe Arg Cys Pro Ser Trp Gln Trp Gln Cys Leu Gly His Asn
1310 1315 1320

Ile Cys Val Asn Leu Ser Val Val Cys Asp Gly Ile Phe Asp Cys
1325 1330 1335

Pro Asn Gly Thr Asp Glu Ser Pro Leu Cys Asn Gly Asn Ser Cys
1340 1345 1350

Ser Asp Phe Asn Gly Gly Cys Thr His Glu Cys Val Gln Glu Pro
1355 1360 1365

Phe Gly Ala Lys Cys Leu Cys Pro Leu Gly Phe Leu Leu Ala Asn
1370 1375 1380

Asp Ser Lys Thr Cys Glu Asp Ile Asp Glu Cys Asp Ile Leu Gly
1385 1390 1395

Ser Cys Ser Gln His Cys Tyr Asn Met Arg Gly Ser Phe Arg Cys
1400 1405 1410

Ser Cys Asp Thr Gly Tyr Met Leu Glu Ser Asp Gly Arg Thr Cys
1415 1420 1425

Lys Val Thr Ala Ser Glu Ser Leu Leu Leu Leu Val Ala Ser Gln
1430 1435 1440

Asn Lys Ile Ile Ala Asp Ser Val Thr Ser Gln Val His Asn Ile
1445 1450 1455

Tyr Ser Leu Val Glu Asn Gly Ser Tyr Ile Val Ala Val Asp Phe
1460 1465 1470

Asp Ser Ile Ser Gly Arg Ile Phe Trp Ser Asp Ala Thr Gln Gly
1475 1480 1485

Lys Thr Trp Ser Ala Phe Gln Asn Gly Thr Asp Arg Arg Val Val
1490 1495 1500

Phe Asp Ser Ser Ile Ile Leu Thr Glu Thr Ile Ala Ile Asp Trp
1505 1510 1515

Val Gly Arg Asn Leu Tyr Trp Thr Asp Tyr Ala Leu Glu Thr Ile
1520 1525 1530

Glu Val Ser Lys Ile Asp Gly Ser His Arg Thr Val Leu Ile Ser
1535 1540 1545

Lys Asn Leu Thr Asn Pro Arg Gly Leu Ala Leu Asp Pro Arg Met
1550 1555 1560

Asn Glu His Leu Leu Phe Trp Ser Asp Trp Gly His His Pro Arg
1565 1570 1575

Ile Glu Arg Ala Ser Met Asp Gly Ser Met Arg Thr Val Ile Val
1580 1585 1590

Gln Asp Lys Ile Phe Trp Pro Cys Gly Leu Thr Ile Asp Tyr Pro
1595 1600 1605

Asn Arg Leu Leu Tyr Phe Met Asp Ser Tyr Leu Asp Tyr Met Asp
1610 1615 1620

Phe Cys Asp Tyr Asn Gly His His Arg Arg Gln Val Ile Ala Ser
1625 1630 1635

Asp Leu Ile Ile Arg His Pro Tyr Ala Leu Thr Leu Phe Glu Asp
1640 1645 1650

Ser Val Tyr Trp Thr Asp Arg Ala Thr Arg Arg Val Met Arg Ala
1655 1660 1665

Asn Lys Trp His Gly Gly Asn Gln Ser Val Val Met Tyr Asn Ile
1670 1675 1680

Gln Trp Pro Leu Gly Ile Val Ala Val His Pro Ser Lys Gln Pro
1685 1690 1695

Asn Ser Val Asn Pro Cys Ala Phe Ser Arg Cys Ser His Leu Cys
1700 1705 1710

Leu Leu Ser Ser Gln Gly Pro His Phe Tyr Ser Cys Val Cys Pro
1715 1720 1725

Ser Gly Trp Ser Leu Ser Pro Asp Leu Leu Asn Cys Leu Arg Asp
1730 1735 1740

Asp Gln Pro Phe Leu Ile Thr Val Arg Gln His Ile Ile Phe Gly
1745 1750 1755

Ile Ser Leu Asn Pro Glu Val Lys Ser Asn Asp Ala Met Val Pro
1760 1765 1770

Ile Ala Gly Ile Gln Asn Gly Leu Asp Val Glu Phe Asp Asp Ala
1775 1780 1785

Glu Gln Tyr Ile Tyr Trp Val Glu Asn Pro Gly Glu Ile His Arg
1790 1795 1800

Val Lys Thr Asp Gly Thr Asn Arg Thr Val Phe Ala Ser Ile Ser
1805 1810 1815

Met Val Gly Pro Ser Met Asn Leu Ala Leu Asp Trp Ile Ser Arg
1820 1825 1830

Asn Leu Tyr Ser Thr Asn Pro Arg Thr Gln Ser Ile Glu Val Leu
1835 1840 1845

Thr Leu His Gly Asp Ile Arg Tyr Arg Lys Thr Leu Ile Ala Asn
1850 1855 1860

Asp Gly Thr Ala Leu Gly Val Gly Phe Pro Ile Gly Ile Thr Val
1865 1870 1875

Asp Pro Ala Arg Gly Lys Leu Tyr Trp Ser Asp Gln Gly Thr Asp
1880 1885 1890

Ser Gly Val Pro Ala Lys Ile Ala Ser Ala Asn Met Asp Gly Thr
1895 1900 1905

Ser Val Lys Thr Leu Phe Thr Gly Asn Leu Glu His Leu Glu Cys
1910 1915 1920

Val Thr Leu Asp Ile Glu Glu Gln Lys Leu Tyr Trp Ala Val Thr
1925 1930 1935

Gly Arg Gly Val Ile Glu Arg Gly Asn Val Asp Gly Thr Asp Arg
1940 1945 1950

Met Ile Leu Val His Gln Leu Ser His Pro Trp Gly Ile Ala Val
1955 1960 1965

His Asp Ser Phe Leu Tyr Tyr Thr Asp Glu Gln Tyr Glu Val Ile
1970 1975 1980

Glu Arg Val Asp Lys Ala Thr Gly Ala Asn Lys Ile Val Leu Arg
1985 1990 1995

Asp Asn Val Pro Asn Leu Arg Gly Leu Gln Val Tyr His Arg Arg
2000 2005 2010

Asn Ala Ala Glu Ser Ser Asn Gly Cys Ser Asn Asn Met Asn Ala
2015 2020 2025

Cys Gln Gln Ile Cys Leu Pro Val Pro Gly Gly Leu Phe Ser Cys
2030 2035 2040

Ala Cys Ala Thr Gly Phe Lys Leu Asn Pro Asp Asn Arg Ser Cys
2045 2050 2055

Ser Pro Tyr Asn Ser Phe Ile Val Val Ser Met Leu Ser Ala Ile
2060 2065 2070

Arg Gly Phe Ser Leu Glu Leu Ser Asp His Ser Glu Thr Met Val
2075 2080 2085

Pro Val Ala Gly Gln Gly Arg Asn Ala Leu His Val Asp Val Asp
2090 2095 2100

Val Ser Ser Gly Phe Ile Tyr Trp Cys Asp Phe Ser Ser Ser Val
2105 2110 2115

Ala Ser Asp Asn Ala Ile Arg Arg Ile Lys Pro Asp Gly Ser Ser
2120 2125 2130

Leu Met Asn Ile Val Thr His Gly Ile Gly Glu Asn Gly Val Arg
2135 2140 2145

Gly Ile Ala Val Asp Trp Val Ala Gly Asn Leu Tyr Phe Thr Asn
2150 2155 2160

Ala Phe Val Ser Glu Thr Leu Ile Glu Val Leu Arg Ile Asn Thr
2165 2170 2175

Thr Tyr Arg Arg Val Leu Leu Lys Val Thr Val Asp Met Pro Arg
2180 2185 2190

His Ile Val Val Asp Pro Lys Asn Arg Tyr Leu Phe Trp Ala Asp
2195 2200 2205

Tyr Gly Gln Arg Pro Lys Ile Glu Arg Ser Phe Leu Asp Cys Thr
2210 2215 2220

Asn Arg Thr Val Leu Val Ser Glu Gly Ile Val Thr Pro Arg Gly
2225 2230 2235

Leu Ala Val Asp Arg Ser Asp Gly Tyr Val Tyr Trp Val Asp Asp
2240 2245 2250

Ser Leu Asp Ile Ile Ala Arg Ile Arg Ile Asn Gly Glu Asn Ser
2255 2260 2265

Glu Val Ile Arg Tyr Gly Ser Arg Tyr Pro Thr Pro Tyr Gly Ile
2270 2275 2280

Thr Val Phe Glu Asn Ser Ile Ile Trp Val Asp Arg Asn Leu Lys
2285 2290 2295

Lys Ile Phe Gln Ala Ser Lys Glu Pro Glu Asn Thr Glu Pro Pro
2300 2305 2310

Thr Val Ile Arg Asp Asn Ile Asn Trp Leu Arg Asp Val Thr Ile
2315 2320 2325

Phe Asp Lys Gln Val Gln Pro Arg Ser Pro Ala Glu Val Asn Asn
2330 2335 2340

Asn Pro Cys Leu Glu Asn Asn Gly Gly Cys Ser His Leu Cys Phe
2345 2350 2355

Ala Leu Pro Gly Leu His Thr Pro Lys Cys Asp Cys Ala Phe Gly
2360 2365 2370

Thr Leu Gln Ser Asp Gly Lys Asn Cys Ala Ile Ser Thr Glu Asn
2375 2380 2385

Phe Leu Ile Phe Ala Leu Ser Asn Ser Leu Arg Ser Leu His Leu
2390 2395 2400

Asp Pro Glu Asn His Ser Pro Pro Phe Gln Thr Ile Asn Val Glu
2405 2410 2415

Arg Thr Val Met Ser Leu Asp Tyr Asp Ser Val Ser Asp Arg Ile
2420 2425 2430

Tyr Phe Thr Gln Asn Leu Ala Ser Gly Val Gly Gln Ile Ser Tyr
2435 2440 2445

Ala Thr Leu Ser Ser Gly Ile His Thr Pro Thr Val Ile Ala Ser
2450 2455 2460

Gly Ile Gly Thr Ala Asp Gly Ile Ala Phe Asp Trp Ile Thr Arg
2465 2470 2475

Arg Ile Tyr Tyr Ser Asp Tyr Leu Asn Gln Met Ile Asn Ser Met
2480 2485 2490

Ala Glu Asp Gly Ser Asn Arg Thr Val Ile Ala Arg Val Pro Lys
2495 2500 2505

Pro Arg Ala Ile Val Leu Asp Pro Cys Gln Gly Tyr Leu Tyr Trp
2510 2515 2520

Ala Asp Trp Asp Thr His Ala Lys Ile Glu Arg Ala Thr Leu Gly
2525 2530 2535

Gly Asn Phe Arg Val Pro Ile Val Asn Ser Ser Leu Val Met Pro
2540 2545 2550

Ser Gly Leu Thr Leu Asp Tyr Glu Glu Asp Leu Leu Tyr Trp Val
2555 2560 2565

Asp Ala Ser Leu Gln Arg Ile Glu Arg Ser Thr Leu Thr Gly Val
2570 2575 2580

Asp Arg Glu Val Ile Val Asn Ala Ala Val His Ala Phe Gly Leu
2585 2590 2595

Thr Leu Tyr Gly Gln Tyr Ile Tyr Trp Thr Asp Leu Tyr Thr Gln
2600 2605 2610

Arg Ile Tyr Arg Ala Asn Lys Tyr Asp Gly Ser Gly Gln Ile Ala
2615 2620 2625

Met Thr Thr Asn Leu Leu Ser Gln Pro Arg Gly Ile Asn Thr Val
2630 2635 2640

Val Lys Asn Gln Lys Gln Gln Cys Asn Asn Pro Cys Glu Gln Phe
2645 2650 2655

Asn Gly Gly Cys Ser His Ile Cys Ala Pro Gly Pro Asn Gly Ala
2660 2665 2670

Glu Cys Gln Cys Pro His Glu Gly Asn Trp Tyr Leu Ala Asn Asn
2675 2680 2685

Arg Lys His Cys Ile Val Asp Asn Gly Glu Arg Cys Gly Ala Ser
2690 2695 2700

Ser Phe Thr Cys Ser Asn Gly Arg Cys Ile Ser Glu Glu Trp Lys
2705 2710 2715

Cys Asp Asn Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu Met Glu
2720 2725 2730

Ser Val Cys Ala Leu His Thr Cys Ser Pro Thr Ala Phe Thr Cys
2735 2740 2745

Ala Asn Gly Arg Cys Val Gln Tyr Ser Tyr Arg Cys Asp Tyr Tyr
2750 2755 2760

Asn Asp Cys Gly Asp Gly Ser Asp Glu Ala Gly Cys Leu Phe Arg
2765 2770 2775

Asp Cys Asn Ala Thr Thr Glu Phe Met Cys Asn Asn Arg Arg Cys
2780 2785 2790

Ile Pro Arg Glu Phe Ile Cys Asn Gly Val Asp Asn Cys His Asp
2795 2800 2805

Asn Asn Thr Ser Asp Glu Lys Asn Cys Pro Asp Arg Thr Cys Gln
2810 2815 2820

Ser Gly Tyr Thr Lys Cys His Asn Ser Asn Ile Cys Ile Pro Arg
2825 2830 2835

Val Tyr Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser Asp
2840 2845 2850

Glu Asn Pro Thr Tyr Cys Ser His Ser His Val Gln Gln Gln
2855 2860 2865

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<400> 74

Met Glu Arg Gly Ala Ala Ala Ala Ala Trp Met Leu Leu Leu Ala Ile
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Ala Ala Cys Leu Glu Pro Val Ser Ser Gln Glu Cys Gly Ser Gly Asn
20 25 30

Phe Arg Cys Asp Asn Gly Tyr Cys Ile Pro Ala Ser Trp Arg Cys Asp
35 40 45

Gly Thr Arg Asp Cys Leu Asp Asp Thr Asp Glu Ile Gly Cys Pro Pro
50 55 60

Arg Ser Cys Glu Ser Gly Leu Phe Leu Cys Pro Ala Glu Gly Thr Cys
65 70 75 80

Ile Pro Ser Ser Trp Val Cys Asp Glu Asp Lys Asp Cys Ser Asp Gly
85 90 95

Ala Asp Glu Gln Gln Asn Cys Ala Gly Thr Thr Cys Ser Ala Gln Gln
100 105 110

Met Thr Cys Ser Asn Gly Gln Cys Ile Pro Ser Glu Tyr Arg Cys Asp
115 120 125

His Val Ser Asp Cys Pro Asp Gly Ser Asp Glu Arg Asn Cys His Tyr
130 135 140

Pro Thr Cys Asp Gln Leu Thr Cys Ala Asn Gly Ala Cys Tyr Asn Thr
145 150 155 160

Ser Gln Arg Cys Asp Gln Lys Val Asp Cys Arg Asp Ser Ser Asp Glu
165 170 175

Ala Asn Cys Thr Thr Leu Cys Ser Gln Lys Glu Phe Glu Cys Gly Ser
180 185 190

Gly Glu Cys Ile Leu Arg Ala Tyr Val Cys Asp His Asp Asn Asp Cys
195 200 205

Glu Asp Asn Ser Asp Glu Arg Asn Cys Asn Tyr Asp Thr Cys Gly Gly
210 215 220

His Gln Phe Thr Cys Ser Asn Gly Gln Cys Ile Asn Gln Asn Trp Val
225 230 235 240

Cys Asp Gly Asp Asp Asp Cys Gln Asp Ser Gly Asp Glu Asp Gly Cys
245 250 255

Glu Ser Asn Gln Ser His His Arg Cys Tyr Pro Arg Glu Trp Ala Cys
260 265 270

Pro Gly Ser Gly Arg Cys Ile Ser Ile Asp Lys Val Cys Asp Gly Val
275 280 285

Pro Asp Cys Pro Glu Gly Asp Asp Glu Asn Asn Val Thr Ser Gly Arg
290 295 300

Thr Cys Gly Met Gly Val Cys Ser Val Leu Asn Cys Glu Tyr Gln Cys
305 310 315 320

His Gln Thr Pro Phe Gly Gly Glu Cys Phe Cys Pro Pro Gly His Ile
325 330 335

Ile Asn Ser Asn Asp Ser Arg Thr Cys Ile Asp Phe Asp Asp Cys Gln
340 345 350

Ile Trp Gly Ile Cys Asp Gln Lys Cys Glu Asn Arg Gln Gly Arg His
355 360 365

Gln Cys Leu Cys Glu Glu Gly Tyr Ile Leu Glu Arg Gly Gln His Cys
370 375 380

Lys Ser Ser Asp Ser Phe Ser Ala Ala Ser Val Ile Phe Ser Asn Gly
385 390 395 400

Arg Asp Leu Leu Val Gly Asp Leu His Gly Arg Asn Phe Arg Ile Leu
405 410 415

Ala Glu Ser Lys Asn Arg Gly Met Val Met Gly Val Asp Phe His Tyr
420 425 430

Gln Lys His Arg Val Phe Trp Thr Asp Pro Met Gln Glu Lys Val Phe
435 440 445

Ser Thr Asp Ile Asn Gly Leu Asn Thr Gln Glu Ile Leu Asn Val Ser
450 455 460

Val Asp Thr Pro Glu Asn Leu Ala Val Asp Trp Ile Asn Asn Lys Leu
465 470 475 480

Tyr Leu Val Glu Thr Lys Val Asn Arg Ile Asp Val Val Asn Leu Glu
485 490 495

Gly Asn Gln Arg Val Thr Leu Ile Thr Glu Asn Leu Gly His Pro Arg
500 505 510

Gly Ile Ala Leu Asp Pro Thr Val Gly Tyr Leu Phe Phe Ser Asp Trp
515 520 525

Gly Ser Leu Ser Gly Gln Pro Lys Val Glu Arg Ala Phe Met Asp Gly
530 535 540

Ser Asn Arg Lys Asp Leu Val Thr Thr Lys Val Gly Trp Pro Ala Gly
545 550 555 560

Ile Thr Leu Asp Leu Val Ser Lys Arg Val Tyr Trp Val Asp Ser Arg
565 570 575

Tyr Asp Tyr Ile Glu Thr Val Thr Tyr Asp Gly Ile Gln Arg Lys Thr
580 585 590

Val Ala Arg Gly Gly Ser Leu Val Pro His Pro Phe Gly Ile Ser Leu
595 600 605

Phe Glu Glu His Val Phe Phe Thr Asp Trp Thr Lys Met Ala Val Met
610 615 620

Lys Ala Ser Lys Phe Thr Glu Thr Asn Pro Gln Val Tyr His Gln Ser
625 630 635 640

Ser Leu Arg Pro His Gly Val Thr Val Tyr His Ala Leu Arg Gln Pro
645 650 655

Asn Ala Thr Asn Pro Cys Gly Ser Asn Asn Gly Gly Cys Ala Gln Val
660 665 670

Cys Val Leu Ser His Arg Thr Asp Asn Gly Gly Leu Gly Tyr Arg Cys
675 680 685

Lys Cys Glu Phe Gly Phe Glu Leu Asp Asp Asp Glu His Arg Cys Val
690 695 700

Ala Val Lys Asn Phe Leu Leu Phe Ser Ser Lys Thr Ala Val Arg Gly
705 710 715 720

Ile Pro Phe Thr Leu Ser Thr Gln Glu Asp Val Met Val Pro Val Thr
725 730 735

Gly Ser Pro Ser Phe Phe Val Gly Ile Asp Phe Asp Ala Gln His Ser
740 745 750

Thr Val Phe Tyr Ser Asp Leu Ser Lys Asp Ile Ile Tyr Lys Gln Lys
755 760 765

Ile Asp Gly Thr Gly Lys Glu Val Ile Thr Ala Asn Arg Leu Glu Ser
770 775 780

Val Glu Cys Leu Thr Phe Asp Trp Ile Ser Arg Asn Leu Tyr Trp Thr
785 790 795 800

Asp Gly Gly Leu Lys Ser Val Thr Val Leu Arg Leu Ala Asp Lys Ser
805 810 815

Arg Arg Gln Ile Ile Ser Asn Leu Asn Asn Pro Arg Ser Ile Val Val
820 825 830

His Pro Thr Ala Gly Tyr Met Phe Leu Ser Asp Trp Phe Arg Pro Ala
835 840 845

Lys Ile Met Arg Ala Trp Ser Asp Gly Ser His Leu Met Pro Ile Val
850 855 860

Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala Ile Asp Trp Ser Ala
865 870 875 880

Ser Arg Leu Tyr Trp Val Asp Ala Phe Phe Asp Lys Ile Glu His Ser
885 890 895

Thr Leu Asp Gly Leu Asp Arg Lys Arg Leu Gly His Val Asp Gln Met
900 905 910

Thr His Pro Phe Gly Leu Thr Val Phe Lys Asp Asn Val Phe Ile Thr
915 920 925

Asp Trp Arg Leu Gly Ala Ile Ile Arg Val Arg Lys Ser Asp Gly Gly
930 935 940

Asp Met Thr Val Ile Arg Arg Gly Ile Ser Ser Val Met His Val Lys
945 950 955 960

Ala Tyr Asp Ala Asp Leu Gln Thr Gly Ser Asn Tyr Cys Ser Gln Thr
965 970 975

Thr His Ala Asn Gly Asp Cys Ser His Phe Cys Phe Pro Val Pro Asn
980 985 990

Phe Gln Arg Val Cys Gly Cys Pro Tyr Gly Met Lys Leu Gln Arg Asp
995 1000 1005

Gln Met Thr Cys Glu Gly Asp Pro Ala Arg Glu Pro Pro Thr Gln
1010 1015 1020

Gln Cys Gly Ser Leu Ser Phe Pro Cys Asn Asn Gly Lys Cys Val
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Pro Ser Phe Phe Arg Cys Asp Gly Val Asp Asp Cys His Asp Asn
1040 1045 1050

Ser Asp Glu His Gln Cys Gly Val Phe Asn Asn Thr Cys Ser Pro
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Ser Ala Phe Ala Cys Val Arg Gly Gly Gln Cys Ile Pro Gly Gln
1070 1075 1080

Trp His Cys Asp Arg Gln Asn Asp Cys Leu Asp Gly Ser Asp Glu
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Gln Asn Cys Pro Thr His Ala Thr Ser Ser Thr Cys Pro Ser Thr
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Ser Phe Thr Cys Asp Asn His Val Cys Ile Pro Lys Asp Trp Val
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Cys Asp Thr Asp Asn Asp Cys Ser Asp Gly Ser Asp Glu Lys Asn
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Cys Gln Ala Ser Gly Thr Cys Gln Pro Thr Gln Phe Arg Cys Pro
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Asp His Arg Cys Ile Ser Pro Leu Tyr Val Cys Asp Gly Asp Lys
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Asp Cys Ala Asp Gly Ser Asp Glu Ala Gly Cys Val Leu Asn Cys
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Thr Ser Ala Gln Phe Lys Cys Ala Asp Gly Ser Ser Cys Ile Asn
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Ser Arg Tyr Arg Cys Asp Gly Val Tyr Asp Cys Arg Asp Asn Ser
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Asp Glu Ala Gly Cys Pro Thr Arg Pro Pro Gly Met Cys His Pro
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Asp Glu Phe Gln Cys Gln Gly Asp Gly Thr Cys Ile Pro Asn Thr
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Trp Glu Cys Asp Gly His Pro Asp Cys Ile His Gly Ser Asp Glu
1250 1255 1260

His Thr Gly Cys Val Pro Lys Thr Cys Ser Pro Thr His Phe Leu
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Cys Asp Asn Gly Asn Cys Ile Tyr Lys Ala Trp Ile Cys Asp Gly
1280 1285 1290

Asp Asn Asp Cys Arg Asp Met Ser Asp Glu Lys Asp Cys Pro Thr
1295 1300 1305

Gln Pro Phe His Cys Pro Ser Thr Gln Trp Gln Cys Pro Gly Tyr
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Ser Thr Cys Ile Asn Leu Ser Ala Leu Cys Asp Gly Val Phe Asp
1325 1330 1335

Cys Pro Asn Gly Thr Asp Glu Ser Pro Leu Cys Asn Gln Asp Ser
1340 1345 1350

Cys Ser His Phe Asn Gly Gly Cys Thr His Gln Cys Met Gln Gly
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Pro Phe Gly Ala Thr Cys Leu Cys Pro Leu Gly Tyr Gln Leu Ala
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Asn Asp Thr Lys Thr Cys Glu Asp Ile Asn Glu Cys Asp Ile Pro
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Gly Phe Cys Ser Gln His Cys Val Asn Met Arg Gly Ser Phe Arg
1400 1405 1410

Cys Ala Cys Asp Pro Glu Tyr Thr Leu Glu Ser Asp Gly Arg Thr
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Cys Lys Val Thr Gly Ser Glu Asn Pro Leu Leu Val Val Ala Ser
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Arg Asp Lys Ile Ile Val Asp Asn Ile Thr Ala His Thr His Asn
1445 1450 1455

Leu Tyr Ser Leu Val Gln Asp Val Ser Phe Val Val Ala Leu Asp
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Phe Asp Ser Val Thr Gly Arg Val Phe Trp Ser Asp Leu Leu Gln
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Gly Lys Thr Trp Ser Val Phe Gln Asn Gly Thr Asp Lys Arg Val
1490 1495 1500

Val His Asp Ser Gly Leu Ser Val Thr Glu Met Ile Ala Val Asp
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Trp Ile Gly Arg Asn Leu Tyr Trp Thr Asp Tyr Ala Leu Glu Thr
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Ile Glu Val Ser Lys Ile Asp Gly Ser His Arg Thr Val Leu Ile
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Ser Lys Asn Val Thr Lys Pro Arg Gly Leu Ala Leu Asp Pro Arg
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Met Gly Asp Asn Val Met Phe Trp Ser Asp Trp Gly His His Pro
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Glu Phe Cys Asp Tyr Asp Gly His Asn Arg Arg Gln Val Ile Ala
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Ser Asp Leu Val Leu His His Pro His Ala Leu Thr Leu Phe Glu
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Ala Asn Lys Trp His Gly Gly Asn Gln Ser Val Val Met Tyr Ser
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Val His Gln Pro Leu Gly Ile Thr Ala Ile His Pro Ser Arg Gln
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Pro Pro Ser Arg Asn Pro Cys Ala Ser Ala Ser Cys Ser His Leu
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Cys Leu Leu Ser Ala Gln Ala Pro Arg His Tyr Ser Cys Ala Cys
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Pro Ser Gly Trp Asn Leu Ser Asp Asp Ser Val Asn Cys Val Arg
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Gly Asp Gln Pro Phe Leu Met Ser Val Arg Asp Asn Ile Ile Phe
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Gly Ile Ser Leu Asp Pro Glu Val Lys Ser Asn Asp Ala Met Val
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Pro Ile Ser Gly Ile Gln His Gly Tyr Asp Val Glu Phe Asp Asp
1775 1780 1785

Ser Glu Gln Phe Ile Tyr Trp Val Glu Asn Pro Gly Glu Ile His
1790 1795 1800

Arg Val Lys Thr Asp Gly Ser Asn Arg Thr Val Phe Ala Pro Leu
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Ser Leu Leu Gly Ser Ser Leu Gly Leu Ala Leu Asp Trp Val Ser
1820 1825 1830

Arg Asn Ile Tyr Tyr Thr Thr Pro Ala Ser Arg Ser Ile Glu Val
1835 1840 1845

Leu Thr Leu Lys Gly Asp Thr Arg Tyr Gly Lys Thr Leu Ile Ala
1850 1855 1860

Asn Asp Gly Thr Pro Leu Gly Val Gly Phe Pro Val Gly Ile Ala
1865 1870 1875

Val Asp Pro Ala Arg Gly Lys Leu Tyr Trp Ser Asp His Gly Thr
1880 1885 1890

Asp Ser Gly Val Pro Ala Lys Ile Ala Ser Ala Asn Met Asp Gly
1895 1900 1905

Thr Ser Leu Lys Ile Leu Phe Thr Gly Asn Leu Gln His Leu Glu
1910 1915 1920

Val Val Thr Leu Asp Ile Gln Glu Gln Lys Leu Tyr Trp Ala Val
1925 1930 1935

Thr Ser Arg Gly Val Ile Glu Arg Gly Asn Val Asp Gly Thr Glu
1940 1945 1950

Arg Met Ile Leu Val His His Leu Ala His Pro Trp Gly Leu Val
1955 1960 1965

Val Tyr Gly Ser Phe Leu Tyr Tyr Ser Asp Glu Gln Tyr Glu Val
1970 1975 1980

Ile Glu Arg Val Asp Lys Ser Ser Gly Asn Asn Lys Val Val Leu
1985 1990 1995

Arg Asp Asn Val Pro Tyr Leu Arg Gly Leu Arg Val Tyr His Arg
2000 2005 2010

Arg Asn Ala Ala Asp Ser Ser Asn Gly Cys Ser Asn Asn Pro Asn
2015 2020 2025

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Cys Ser Pro Tyr Asn Ser Phe Met Val Val Ser Met Leu Pro Ala
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Val Arg Ser Ser Asn Gly Ile Arg Arg Ile Lys Pro Asp Gly Ser
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Arg Gly Val Ala Leu Asp Trp Ala Ala Gly Asn Leu Tyr Phe Thr
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Arg His Ile Ile Val Asp Pro Lys His Arg Tyr Leu Phe Trp Ala
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Gly Leu Ala Met Asp His Asp Thr Gly Tyr Ile Tyr Trp Val Asp
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Asp Ser Leu Asp Leu Ile Ala Arg Ile His Leu Asp Gly Gly Glu
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Ser Gln Val Val Arg Tyr Gly Ser Arg Tyr Pro Thr Pro Tyr Gly
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Ile Thr Val Phe Gly Glu Ser Ile Ile Trp Val Asp Arg Asn Leu
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Lys Lys Val Phe Gln Ala Ser Lys Gln Pro Gly Asn Thr Asp Pro
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Pro Val Val Ile Arg Asp Lys Ile Asn Leu Leu Arg Asp Val Thr
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Ile Phe Asp Glu His Ala Gln Pro Leu Ser Pro Ala Glu Leu Asn
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Gly Thr Leu Gly Asn Asp Gly Lys Ser Cys Ala Thr Ser Gln Glu
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Ala Gly Thr Ala Ile Ala Leu Asp Tyr Asp Arg Arg Asn Asn Arg
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Met Ala Glu Asp Gly Ser Asn Arg Ala Val Ile Ala Arg Val Ser
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Lys Pro Arg Ala Ile Val Leu Asp Pro Cys Arg Gly Tyr Met Tyr
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Gly Gly Asn Phe Arg Val Pro Ile Val Asn Thr Ser Leu Val Trp
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Pro Asn Gly Leu Ala Leu Asp Leu Glu Thr Asp Leu Leu Tyr Trp
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Ala Asp Ala Ser Leu Gln Lys Ile Glu Arg Ser Thr Leu Thr Gly
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Leu Thr Val Tyr Gly Gln Tyr Ile Tyr Trp Thr Asp Leu Tyr Thr
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Arg Lys Ile Tyr Arg Ala Asn Lys Tyr Asp Gly Ser Asp Leu Val
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Ala Met Thr Thr Arg Leu Pro Thr Gln Pro Ser Gly Ile Ser Thr
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Val Val Lys Thr Gln Arg Gln Gln Cys Ser Asn Pro Cys Asp Gln
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Phe Asn Gly Gly Cys Ser His Ile Cys Ala Pro Gly Pro Asn Gly
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His Cys Glu Leu Gln Asn Cys Ser Ser Thr Gln Phe Thr Cys Val
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Asp Cys Gly Asp Tyr Ser Asp Glu Arg Gly Cys Ser Tyr Pro Pro
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Leu His Gln Phe Arg Cys Asp Asn Gly His Cys Ile Glu Met Gly
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Arg Val Cys Asn His Val Asp Asp Cys Ser Asp Asn Ser Asp Glu
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Lys Gly Cys Gly Ile Asn Glu Cys Leu Asp Ser Ser Ile Ser Arg
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Cys Asp His Asn Cys Thr Asp Thr Ile Thr Ser Phe Tyr Cys Ser
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Cys Leu Pro Gly Tyr Lys Leu Met Ser Asp Lys Arg Ser Cys Val
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<213> MOUSE

<400> 75

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Gly Val Lys Leu Glu Ser Thr Ile Val Ala Ser Gly Leu Glu Asp Ala
50 55 60

Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr Asp
65 70 75 80

Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly Ala
85 90 95

Ala Ala Gln Asn Ile Val Ile Ser Gly Leu Val Ser Pro Asp Gly Leu
100 105 110

Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu Thr
115 120 125

Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val Leu
130 135 140

Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro Ala
145 150 155 160

His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Ala Pro Arg Ile Glu
165 170 175

Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser Asp
180 185 190

Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys Leu
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Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His His Ala Asn Leu Asp
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Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro Phe
225 230 235 240

Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln Thr
245 250 255

Arg Ser Ile His Ala Cys Asn Lys Trp Thr Gly Glu Gln Arg Lys Glu
260 265 270

Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser Gln
275 280 285

Glu Arg Gln Pro Pro Phe His Thr Pro Cys Glu Glu Asp Asn Gly Gly
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Cys Ser His Leu Cys Leu Leu Ser Pro Arg Glu Pro Phe Tyr Ser Cys
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Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Lys Thr Cys Lys
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Thr Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu Arg
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Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln Val
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Gly Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu Gly
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Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala Tyr
385 390 395 400

Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn Asp
405 410 415

Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp Thr
420 425 430

Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr Ser
435 440 445

Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile Val
450 455 460

Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu Asn
465 470 475 480

Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Arg Asp Arg His Val Leu
485 490 495

Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu Gln
500 505 510

Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu Val
515 520 525

Ile Asn Ile Asp Gly Thr Lys Arg Lys Thr Leu Leu Glu Asp Lys Leu
530 535 540

Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp Thr
545 550 555 560

Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala Ser
565 570 575

Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys Ala
580 585 590

Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Gly Asn
595 600 605

Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro Arg Ala Thr Lys Cys
610 615 620

Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys Ile
625 630 635 640

Ile Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Thr Ile His Arg
645 650 655

Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr Gly
660 665 670

Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His Ile
675 680 685

Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met Asn
690 695 700

Gly Ser Ser Val Glu His Val Ile Glu Phe Gly Leu Asp Tyr Pro Glu
705 710 715 720

Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp Thr
725 730 735

Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg Gln
740 745 750

Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu Asp
755 760 765

Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro Arg
770 775 780

Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val Asp
785 790 795 800

Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln Arg
805 810 815

Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn Met
820 825 830

Leu Gly Gln Glu Arg Met Val Ile Ala Asp Asp Leu Pro Tyr Pro Phe
835 840 845

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Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn Leu
    850                 855                 860

His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr Leu
865                 870                 875                 880

Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His Ser
                885                 890                 895

Ser Arg Gln Asp Gly Leu Asn Asp Cys Val His Ser Asn Gly Gln Cys
            900                 905                 910

Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys Ala
        915                 920                 925

Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro Ser
    930                 935                 940

Thr Phe Leu Leu Phe Ser Gln Lys Phe Ala Ile Ser Arg Met Ile Pro
945                 950                 955                 960

Asp Asp Gln Leu Ser Pro Asp Leu Val Leu Pro Leu His Gly Leu Arg
                965                 970                 975

Asn Val Lys Ala Ile Asn Tyr Asp Pro Leu Asp Lys Phe Ile Tyr Trp
            980                 985                 990

Val Asp Gly Arg Gln Asn Ile Lys  Arg Ala Lys Asp Asp  Gly Thr Gln
        995                 1000                1005

Pro Ser  Met Leu Thr Ser Pro  Ser Gln Ser Leu Ser  Pro Asp Arg
    1010                1015                1020

Gln Pro  His Asp Leu Ser Ile  Asp Ile Tyr Ser Arg  Thr Leu Phe
    1025                1030                1035

Trp Thr  Cys Glu Ala Thr Asn  Thr Ile Asn Val His  Arg Leu Asp
    1040                1045                1050

Gly Asp  Ala Met Gly Val Val  Leu Arg Gly Asp Arg  Asp Lys Pro
    1055                1060                1065

Arg Ala  Ile Ala Val Asn Ala  Glu Arg Gly Tyr Met  Tyr Phe Thr
    1070                1075                1080

Asn Met  Gln Asp His Ala Ala  Lys Ile Glu Arg Ala  Ser Leu Asp
    1085                1090                1095

Gly Thr  Glu Arg Glu Val Leu  Phe Thr Thr Gly Leu  Ile Arg Pro
    1100                1105                1110
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Val Ala Leu Val Val Asp Asn Ala Leu Gly Lys Leu Phe Trp Val
1115 1120 1125

Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly Ala
1130 1135 1140

Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Val Gly
1145 1150 1155

Leu Thr Val Leu Gly Arg His Leu Tyr Trp Ile Asp Arg Gln Gln
1160 1165 1170

Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg Thr
1175 1180 1185

Arg Val Gln Gly Arg Val Thr His Leu Thr Gly Ile His Ala Val
1190 1195 1200

Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala Arg
1205 1210 1215

Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly Asp Gly
1220 1225 1230

Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln Asn
1235 1240 1245

Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln Phe
1250 1255 1260

Ala Cys Thr Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp Arg
1265 1270 1275

Cys Asp Gly Phe Pro Glu Cys Ala Asp Gln Ser Asp Glu Glu Gly
1280 1285 1290

Cys Pro Val Cys Ser Ala Ser Gln Phe Pro Cys Ala Arg Gly Gln
1295 1300 1305

Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys Gln
1310 1315 1320

Asp Arg Ser Asp Glu Ala Asn Cys Asp Ala Val Cys Leu Pro Asn
1325 1330 1335

Gln Phe Arg Cys Thr Ser Gly Gln Cys Val Leu Ile Lys Gln Gln
1340 1345 1350

Cys Asp Ser Phe Pro Asp Cys Ala Asp Gly Ser Asp Glu Leu Met
1355 1360 1365

Cys Glu Ile Asn Lys Pro Pro Ser Asp Asp Ile Pro Ala His Ser
1370 1375 1380

Ser Ala Ile Gly Pro Val Ile Gly Ile Ile Leu Ser Leu Phe Val
1385 1390 1395

Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Met Cys Gln Arg
1400 1405 1410

Tyr Thr Gly Ala Ser Gly Pro Phe Pro His Glu Tyr Val Gly Gly
1415 1420 1425

Ala Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser Gln
1430 1435 1440

His Gly Pro Phe Pro Gly Ile Pro Cys Ser Lys Ser Val Met Ser
1445 1450 1455

Ser Met Ser Leu Val Gly Gly Arg Gly Ser Val Pro Leu Tyr Asp
1460 1465 1470

Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser Thr
1475 1480 1485

Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser Pro
1490 1495 1500

Ala Thr Asp Pro Ser Leu Tyr Asn Val Asp Val Phe Tyr Ser Ser
1505 1510 1515

Gly Ile Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Val Ile Arg
1520 1525 1530

Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp
1535 1540 1545

Ser Asp Tyr Ser Ile Ser Arg Trp Lys Ser Ser Lys Tyr Tyr Leu
1550 1555 1560

Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro
1565 1570 1575

His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro
1580 1585 1590

Gly Thr Glu Arg Ser Tyr Cys His Leu Phe Pro Pro Pro Pro Ser
1595 1600 1605

Pro Cys Thr Asp Ser Ser
1610

<210> 76
<211> 770
<212> PRT
<213> HOMO SAPIENS

<400> 76

Met Glu Lys Arg Ala Ala Ala Gly Leu Glu Gly Ala Pro Gly Ala Arg
1 5 10 15

Ala Gln Leu Ala Val Val Cys Leu Val Asn Ile Phe Leu Thr Gly Arg
20 25 30

Leu Ser Ser Ala Val Pro Ala Leu Ala Ala Cys Ser Gly Lys Leu Glu
35 40 45

Gln His Thr Glu Arg Arg Gly Val Ile Tyr Ser Pro Ala Trp Pro Leu
50 55 60

Asn Tyr Pro Pro Gly Thr Asn Cys Ser Trp Tyr Ile Gln Gly Asp Arg
65 70 75 80

Gly Asp Met Ile Thr Ile Ser Phe Arg Asn Phe Asp Val Glu Glu Ser
85 90 95

His Gln Cys Ser Leu Asp Trp Leu Leu Leu Gly Pro Ala Ala Pro Pro
100 105 110

Arg Gln Glu Ala Phe Arg Leu Cys Gly Ser Ala Ile Pro Pro Ala Phe
115 120 125

Ile Ser Ala Arg Asp His Val Trp Ile Phe Phe His Ser Asp Ala Ser
130 135 140

Ser Ser Gly Gln Ala Gln Gly Phe Arg Leu Ser Tyr Ile Arg Gly Lys
145 150 155 160

Leu Gly Gln Ala Ser Cys Gln Ala Asp Glu Phe Arg Cys Asp Asn Gly
165 170 175

Lys Cys Leu Pro Gly Pro Trp Gln Cys Asn Thr Val Asp Glu Cys Gly
180 185 190

Asp Gly Ser Asp Glu Gly Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro
195 200 205

Gly Ser Leu Cys Pro Gly Gly Thr Phe Pro Cys Ser Gly Ala Arg Ser
210 215 220

Thr Arg Cys Leu Pro Val Glu Arg Arg Cys Asp Gly Leu Gln Asp Cys
225 230 235 240

Gly Asp Gly Ser Asp Glu Ala Gly Cys Pro Asp Leu Ala Cys Gly Arg

245 250 255

Arg Leu Gly Ser Phe Tyr Gly Ser Phe Ala Ser Pro Asp Leu Phe Gly
260 265 270

Ala Ala Arg Gly Pro Ser Asp Leu His Cys Thr Trp Leu Val Asp Thr
275 280 285

Gln Asp Ser Arg Arg Val Leu Leu Gln Leu Glu Leu Arg Leu Gly Tyr
290 295 300

Asp Asp Tyr Val Gln Val Tyr Glu Gly Leu Gly Glu Arg Gly Asp Arg
305 310 315 320

Leu Leu Gln Thr Leu Ser Tyr Arg Ser Asn His Arg Pro Val Ser Leu
325 330 335

Glu Ala Ala Gln Gly Arg Leu Thr Val Ala Tyr His Ala Arg Ala Arg
340 345 350

Ser Ala Gly His Gly Phe Asn Ala Thr Tyr Gln Val Lys Gly Tyr Cys
355 360 365

Leu Pro Trp Glu Gln Pro Cys Gly Ser Ser Ser Asp Ser Asp Gly Gly
370 375 380

Ser Leu Gly Asp Gln Gly Cys Phe Ser Glu Pro Gln Arg Cys Asp Gly
385 390 395 400

Trp Trp His Cys Ala Ser Gly Arg Asp Glu Gln Gly Cys Pro Ala Cys
405 410 415

Pro Pro Asp Gln Tyr Pro Cys Glu Gly Gly Ser Gly Leu Cys Tyr Thr
420 425 430

Pro Ala Asp Arg Cys Asn Asn Gln Lys Ser Cys Pro Asp Gly Ala Asp
435 440 445

Glu Lys Asn Cys Phe Ser Cys Gln Pro Gly Thr Phe His Cys Gly Thr
450 455 460

Asn Leu Cys Ile Phe Glu Thr Trp Arg Cys Asp Gly Gln Glu Asp Cys
465 470 475 480

Gln Asp Gly Ser Asp Glu His Gly Cys Leu Ala Ala Val Pro Arg Lys
485 490 495

Val Ile Thr Ala Ala Leu Ile Gly Ser Leu Val Cys Gly Leu Leu Leu
500 505 510

Val Ile Ala Leu Gly Cys Ala Phe Lys Leu Tyr Ser Leu Arg Thr Gln

515 520 525

Glu Tyr Arg Ala Phe Glu Thr Gln Met Thr Arg Leu Glu Ala Glu Phe
530 535 540

Val Arg Arg Glu Ala Pro Pro Ser Tyr Gly Gln Leu Ile Ala Gln Gly
545 550 555 560

Leu Ile Pro Pro Val Glu Asp Phe Pro Val Tyr Ser Ala Ser Gln Ala
565 570 575

Ser Val Leu Gln Asn Leu Arg Thr Ala Met Arg Arg Gln Met Arg Arg
580 585 590

His Ala Ser Arg Arg Gly Pro Ser Arg Arg Arg Leu Gly Arg Leu Trp
595 600 605

Asn Arg Leu Phe His Arg Pro Arg Ala Pro Arg Gly Gln Ile Pro Leu
610 615 620

Leu Thr Ala Ala Arg Pro Ser Gln Thr Val Leu Gly Asp Gly Phe Leu
625 630 635 640

Gln Pro Ala Pro Gly Ala Ala Pro Asp Pro Pro Ala Pro Leu Met Asp
645 650 655

Thr Gly Ser Thr Arg Ala Ala Gly Asp Arg Pro Pro Ser Ala Pro Gly
660 665 670

Arg Ala Pro Glu Val Gly Pro Ser Gly Pro Pro Leu Pro Ser Gly Leu
675 680 685

Arg Asp Pro Glu Cys Arg Pro Val Asp Lys Asp Arg Lys Val Cys Arg
690 695 700

Glu Pro Leu Val Asp Gly Pro Ala Pro Ala Asp Ala Pro Arg Glu Pro
705 710 715 720

Cys Ser Ala Gln Asp Pro His Pro Gln Val Ser Thr Ala Ser Ser Thr
725 730 735

Leu Gly Pro His Ser Pro Glu Pro Leu Gly Val Cys Arg Asn Pro Pro
740 745 750

Pro Pro Cys Ser Pro Met Leu Glu Ala Ser Asp Asp Glu Ala Leu Leu
755 760 765

Val Cys
770

<210> 77

<211> 770
<212> PRT
<213> RAT

<400> 77

Met Glu Lys Arg Ala Ala Ala Gly Pro Glu Gly Ala Pro Gly Ala Arg
1 5 10 15

Ala Pro Leu Ala Val Val Cys Leu Val Asn Leu Phe Leu Thr Gly Arg
20 25 30

Leu Ser Ser Ala Val Pro Ala Leu Ala Ala Cys Ser Gly Lys Leu Glu
35 40 45

Gln His Thr Glu Arg Arg Gly Val Ile Tyr Ser Pro Ala Trp Pro Leu
50 55 60

Asn Tyr Pro Pro Gly Thr Asn Cys Ser Trp Tyr Ile Gln Gly Asp Arg
65 70 75 80

Gly Asp Met Ile Thr Ile Ser Phe Arg Asn Phe Asp Val Glu Glu Ser
85 90 95

His Gln Cys Ser Leu Asp Trp Leu Leu Leu Gly Pro Ala Ala Pro Pro
100 105 110

Arg Gln Glu Ala Phe Arg Leu Cys Gly Ser Ala Ile Pro Pro Ala Phe
115 120 125

Ile Ser Ala Arg Asp His Val Trp Ile Phe Phe His Ser Asp Ala Ser
130 135 140

Ser Ser Gly Gln Ala Gln Gly Phe Arg Leu Ser Tyr Ile Arg Gly Lys
145 150 155 160

Leu Gly Gln Ala Ser Cys Gln Thr Asp Glu Phe Arg Cys Asp Asn Gly
165 170 175

Lys Cys Leu Pro Gly Pro Trp Gln Cys Asn Met Val Asp Glu Cys Gly
180 185 190

Asp Gly Ser Asp Glu Gly Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro
195 200 205

Gly Ser Leu Cys Pro Gly Gly Thr Phe Pro Cys Ser Gly Ala Arg Ser
210 215 220

Thr Arg Cys Leu Pro Val Glu Arg Arg Cys Asp Gly Thr Gln Asp Cys
225 230 235 240

Gly Asp Gly Ser Asp Glu Ala Gly Cys Pro Asp Leu Ala Cys Gly Arg
245 250 255

Arg Leu Gly Ser Phe Tyr Gly Ser Phe Ala Ser Pro Asp Leu Phe Gly
260 265 270

Ala Ala Arg Gly Pro Ser Asp Leu His Cys Thr Trp Leu Val Asp Thr
275 280 285

Gln Asp Pro Arg Arg Val Leu Leu Gln Leu Glu Leu Arg Leu Gly Tyr
290 295 300

Asp Asp Tyr Val Gln Val Tyr Glu Gly Leu Gly Glu Arg Gly Asp Arg
305 310 315 320

Leu Leu Gln Thr Leu Ser Tyr Arg Ser Asn His Arg Pro Val Ser Leu
325 330 335

Glu Ala Ala Gln Gly Arg Leu Thr Val Ala Tyr His Ala Arg Ala Arg
340 345 350

Ser Ala Gly His Gly Phe Asn Ala Thr Tyr Gln Val Lys Gly Tyr Cys
355 360 365

Leu Pro Trp Glu Gln Pro Cys Gly Ser Ser Ser Glu Gly Asp Asp Gly
370 375 380

Ser Thr Gly Glu Gln Gly Cys Phe Ser Glu Pro Gln Arg Cys Asp Gly
385 390 395 400

Trp Trp His Cys Ala Ser Gly Arg Asp Glu Gln Gly Cys Pro Ala Cys
405 410 415

Pro Pro Asp Gln Tyr Pro Cys Glu Gly Gly Ser Gly Leu Cys Tyr Ala
420 425 430

Pro Ala Asp Arg Cys Asn Asn Gln Lys Ser Cys Pro Asp Gly Ala Asp
435 440 445

Glu Lys Asn Cys Phe Ser Cys Gln Pro Gly Thr Phe His Cys Gly Thr
450 455 460

Asn Leu Cys Ile Phe Glu Thr Trp Arg Cys Asp Gly Gln Glu Asp Cys
465 470 475 480

Gln Asp Gly Ser Asp Glu His Gly Cys Leu Ala Ala Val Pro Arg Lys
485 490 495

Val Ile Thr Ala Ala Leu Ile Gly Ser Leu Val Cys Gly Leu Leu Leu
500 505 510

Val Ile Ala Leu Gly Cys Ala Phe Lys Leu Tyr Ser Leu Arg Thr Gln
515 520 525

Glu Tyr Arg Ala Phe Glu Thr Gln Met Thr Arg Leu Glu Ala Glu Phe
530 535 540

Val Arg Arg Glu Ala Pro Pro Ser Tyr Gly Gln Leu Ile Ala Gln Gly
545 550 555 560

Leu Ile Pro Pro Val Glu Asp Phe Pro Val Tyr Ser Ala Ser Gln Ala
565 570 575

Ser Val Leu Gln Asn Leu Arg Thr Ala Met Arg Arg Gln Met Arg Arg
580 585 590

His Ala Ser Arg Arg Gly Pro Ser Arg Arg Arg Leu Gly Arg Leu Trp
595 600 605

Asn Arg Leu Phe His Arg Pro Arg Ala Pro Arg Gly Gln Ile Pro Leu
610 615 620

Leu Thr Ala Ala Arg Thr Ser Gln Thr Val Leu Gly Asp Gly Leu Leu
625 630 635 640

Gln Ala Ala Pro Gly Pro Val Pro Asp Pro Pro Val Pro Asn Thr Asp
645 650 655

Thr Gly Ser Pro Arg Glu Ala Gly Asp Gly Pro Pro Ser Gly Ser Gly
660 665 670

His Ala Pro Glu Val Gly Pro Ser Val Pro Pro Pro Pro Leu Asn Leu
675 680 685

Arg Asp Pro Glu Tyr Arg Pro Glu Asp Lys Glu Arg Lys Ala Cys Val
690 695 700

Asp Pro Leu Glu Asp Ser Pro Ala Pro Val Asp Thr Pro Pro Glu Pro
705 710 715 720

Cys Leu Ala Gln Asp Pro His Pro Gln Thr Pro Thr Ala Ser Gly Ile
725 730 735

Gln Asp Pro His Ser Ala Glu Pro Leu Gly Val Cys Arg Ser Pro Pro
740 745 750

Pro Thr Cys Ser Pro Ile Leu Glu Ala Ser Asp Asp Glu Ala Leu Leu
755 760 765

Val Cys
770

<210> 78
<211> 1113

<212> PRT
<213> MOUSE

<400> 78

Met Gly Arg Val Ser Phe Ser Val Arg Val Ser Ser Val Arg Arg Ala
1 5 10 15

Arg Cys Ser Cys Pro Gly Arg Cys Tyr Leu Ser Cys Arg Val Pro Pro
20 25 30

Thr Thr Ala Leu Arg Ala Leu Asn Gly Leu Gly Cys Ala Gly Val Pro
35 40 45

Gly Glu Thr Ala Gly Gly Ala Val Gly Pro Gly Pro Leu Gly Thr Arg
50 55 60

Gly Phe Leu Ser Gly Ser Lys Phe Gln Ala Pro Gly Ser Trp Lys Asp
65 70 75 80

Cys Phe Gly Ala Pro Pro Ala Pro Asp Val Leu Arg Ala Asp Arg Ser
85 90 95

Val Gly Glu Gly Cys Pro Gln Lys Leu Val Thr Ala Asn Leu Leu Arg
100 105 110

Phe Leu Leu Leu Val Leu Ile Pro Cys Ile Cys Ala Leu Ile Val Leu
115 120 125

Leu Ala Ile Leu Leu Ser Phe Val Gly Thr Leu Lys Arg Val Tyr Phe
130 135 140

Lys Ser Asn Asp Ser Glu Pro Leu Val Thr Asp Gly Glu Ala Arg Val
145 150 155 160

Pro Gly Val Ile Pro Val Asn Thr Val Tyr Tyr Glu Asn Thr Gly Ala
165 170 175

Pro Ser Leu Pro Pro Ser Gln Ser Thr Pro Ala Trp Thr Pro Arg Ala
180 185 190

Pro Ser Pro Glu Asp Gln Ser His Arg Asn Thr Ser Thr Cys Met Asn
195 200 205

Ile Thr His Ser Gln Cys Gln Ile Leu Pro Tyr His Ser Thr Leu Ala
210 215 220

Pro Leu Leu Pro Ile Val Lys Asn Met Asp Met Glu Lys Phe Leu Lys
225 230 235 240

Phe Phe Thr Tyr Leu His Arg Leu Ser Cys Tyr Gln His Ile Leu Leu
245 250 255

Phe Gly Cys Ser Leu Ala Phe Pro Glu Cys Val Val Asp Gly Asp Asp
260 265 270

Arg His Gly Leu Leu Pro Cys Arg Ser Phe Cys Glu Ala Ala Lys Glu
275 280 285

Gly Cys Glu Ser Val Leu Gly Met Val Asn Ser Ser Trp Pro Asp Ser
290 295 300

Leu Arg Cys Ser Gln Phe Arg Asp His Thr Glu Thr Asn Ser Ser Val
305 310 315 320

Arg Lys Ser Cys Phe Ser Leu Gln Gln Glu His Gly Lys Gln Ser Leu
325 330 335

Cys Gly Gly Gly Glu Ser Phe Leu Cys Thr Ser Gly Leu Cys Val Pro
340 345 350

Lys Lys Leu Gln Cys Asn Gly Tyr Asn Asp Cys Asp Asp Trp Ser Asp
355 360 365

Glu Ala His Cys Asn Cys Ser Lys Asp Leu Phe His Cys Gly Thr Gly
370 375 380

Lys Cys Leu His Tyr Ser Leu Leu Cys Asp Gly Tyr Asp Asp Cys Gly
385 390 395 400

Asp Pro Ser Asp Glu Gln Asn Cys Asp Cys Asn Leu Thr Lys Glu His
405 410 415

Arg Cys Gly Asp Gly Arg Cys Ile Ala Ala Glu Trp Val Cys Asp Gly
420 425 430

Asp His Asp Cys Val Asp Lys Ser Asp Glu Val Asn Cys Ser Cys His
435 440 445

Ser Gln Gly Leu Val Glu Cys Thr Ser Gly Gln Cys Ile Pro Ser Thr
450 455 460

Phe Gln Cys Asp Gly Asp Glu Asp Cys Lys Asp Gly Ser Asp Glu Glu
465 470 475 480

Asn Cys Ser Asp Ser Gln Thr Pro Cys Pro Glu Gly Glu Gln Gly Cys
485 490 495

Phe Gly Ser Ser Cys Val Glu Ser Cys Ala Gly Ser Ser Leu Cys Asp
500 505 510

Ser Asp Ser Ser Leu Ser Asn Cys Ser Gln Cys Glu Pro Ile Thr Leu
515 520 525

Glu Leu Cys Met Asn Leu Leu Tyr Asn His Thr His Tyr Pro Asn Tyr
530 535 540

Leu Gly His Arg Thr Gln Lys Glu Ala Ser Ile Ser Trp Glu Ser Ser
545 550 555 560

Leu Phe Pro Ala Leu Val Gln Thr Asn Cys Tyr Lys Tyr Leu Met Phe
565 570 575

Phe Ala Cys Thr Ile Leu Val Pro Lys Cys Asp Val Asn Thr Gly Gln
580 585 590

Arg Ile Pro Pro Cys Arg Leu Leu Cys Glu His Ser Lys Glu Arg Cys
595 600 605

Glu Ser Val Leu Gly Ile Val Gly Leu Gln Trp Pro Glu Asp Thr Asp
610 615 620

Cys Asn Gln Phe Pro Glu Glu Ser Ser Asp Asn Gln Thr Cys Leu Leu
625 630 635 640

Pro Asn Glu Asp Val Glu Glu Cys Ser Pro Ser His Phe Lys Cys Arg
645 650 655

Ser Gly Arg Cys Val Leu Gly Ser Arg Arg Cys Asp Gly Gln Ala Asp
660 665 670

Cys Asp Asp Asp Ser Asp Glu Glu Asn Cys Gly Cys Lys Glu Arg Ala
675 680 685

Leu Trp Glu Cys Pro Phe Asn Lys Gln Cys Leu Lys His Thr Leu Ile
690 695 700

Cys Asp Gly Phe Pro Asp Cys Pro Asp Ser Met Asp Glu Lys Asn Cys
705 710 715 720

Ser Phe Cys Gln Asp Asn Glu Leu Glu Cys Ala Asn His Glu Cys Val
725 730 735

Pro Arg Asp Leu Trp Cys Asp Gly Trp Val Asp Cys Ser Asp Ser Ser
740 745 750

Asp Glu Trp Gly Cys Val Thr Leu Ser Lys Asn Gly Asn Ser Ser Ser
755 760 765

Leu Leu Thr Val His Lys Ser Ala Lys Glu His His Val Cys Ala Asp
770 775 780

Gly Trp Arg Glu Thr Leu Ser Gln Leu Ala Cys Lys Gln Met Gly Leu
785 790 795 800

Gly Glu Pro Ser Val Thr Lys Leu Ile Pro Gly Gln Glu Gly Gln Gln
805 810 815

Trp Leu Arg Leu Tyr Pro Asn Trp Glu Asn Leu Asn Gly Ser Thr Leu
820 825 830

Gln Glu Leu Leu Val Tyr Arg His Ser Cys Pro Ser Arg Ser Glu Ile
835 840 845

Ser Leu Leu Cys Ser Lys Gln Asp Cys Gly Arg Arg Pro Ala Ala Arg
850 855 860

Met Asn Lys Arg Ile Leu Gly Gly Arg Thr Ser Arg Pro Gly Arg Trp
865 870 875 880

Pro Trp Gln Cys Ser Leu Gln Ser Glu Pro Ser Gly His Ile Cys Gly
885 890 895

Cys Val Leu Ile Ala Lys Lys Trp Val Leu Thr Val Ala His Cys Phe
900 905 910

Glu Gly Arg Glu Asp Ala Asp Val Trp Lys Val Val Phe Gly Ile Asn
915 920 925

Asn Leu Asp His Pro Ser Gly Phe Met Gln Thr Arg Phe Val Lys Thr
930 935 940

Ile Leu Leu His Pro Arg Tyr Ser Arg Ala Val Val Asp Tyr Asp Ile
945 950 955 960

Ser Val Val Glu Leu Ser Asp Asp Ile Asn Glu Thr Ser Tyr Val Arg
965 970 975

Pro Val Cys Leu Pro Ser Pro Glu Glu Tyr Leu Glu Pro Asp Thr Tyr
980 985 990

Cys Tyr Ile Thr Gly Trp Gly His Met Gly Asn Lys Met Pro Phe Lys
995 1000 1005

Leu Gln Glu Gly Glu Val Arg Ile Ile Pro Leu Glu Gln Cys Gln
1010 1015 1020

Ser Tyr Phe Asp Met Lys Thr Ile Thr Asn Arg Met Ile Cys Ala
1025 1030 1035

Gly Tyr Glu Ser Gly Thr Val Asp Ser Cys Met Gly Asp Ser Gly
1040 1045 1050

Gly Pro Leu Val Cys Glu Arg Pro Gly Gly Gln Trp Thr Leu Phe
1055 1060 1065

Gly Leu Thr Ser Trp Gly Ser Val Cys Phe Ser Lys Val Leu Gly
1070 1075 1080

Pro Gly Val Tyr Ser Asn Val Ser Tyr Phe Val Gly Trp Ile Glu
1085 1090 1095

Arg Gln Ile Tyr Ile Gln Thr Phe Leu Gln Lys Lys Ser Gln Gly
1100 1105 1110

<210> 79
<211> 859
<212> PRT
<213> HOMO SAPIENS

<400> 79

Met Asn Ser Phe Leu Ile Phe Ala Arg Arg Ile Asp Ile Arg Met Val
1 5 10 15

Ser Leu Asp Ile Pro Tyr Phe Ala Asp Val Val Val Pro Ile Asn Ile
20 25 30

Thr Met Lys Asn Thr Ile Ala Ile Gly Val Asp Pro Gln Glu Gly Lys
35 40 45

Val Tyr Trp Ser Asp Ser Thr Leu His Arg Ile Ser Arg Ala Asn Leu
50 55 60

Asp Gly Ser Gln His Glu Asp Ile Ile Thr Thr Gly Leu Gln Thr Thr
65 70 75 80

Asp Gly Leu Ala Val Asp Ala Ile Gly Arg Lys Val Tyr Trp Thr Asp
85 90 95

Thr Gly Thr Asn Arg Ile Glu Val Gly Asn Leu Asp Gly Ser Met Arg
100 105 110

Lys Val Leu Val Trp Gln Asn Leu Asp Ser Pro Arg Ala Ile Val Leu
115 120 125

Tyr His Glu Met Gly Phe Met Tyr Trp Thr Asp Trp Gly Glu Asn Ala
130 135 140

Lys Leu Glu Arg Ser Gly Met Asp Gly Ser Asp Arg Ala Val Leu Ile
145 150 155 160

Asn Asn Asn Leu Gly Trp Pro Asn Gly Leu Thr Val Asp Lys Ala Ser
165 170 175

Ser Gln Leu Leu Trp Ala Asp Ala His Thr Glu Arg Ile Glu Ala Ala
180 185 190

Asp Leu Asn Gly Ala Asn Arg His Thr Leu Val Ser Pro Val Gln His
195 200 205

Pro Tyr Gly Leu Thr Leu Leu Asp Ser Tyr Ile Tyr Trp Thr Asp Trp
210 215 220

Gln Thr Arg Ser Ile His Arg Ala Asp Lys Gly Thr Gly Ser Asn Val
225 230 235 240

Ile Leu Val Arg Ser Asn Leu Pro Gly Leu Met Asp Met Gln Ala Val
245 250 255

Asp Arg Ala Gln Pro Leu Gly Phe Asn Lys Cys Gly Ser Arg Asn Gly
260 265 270

Gly Cys Ser His Leu Cys Leu Pro Arg Pro Ser Gly Phe Ser Cys Ala
275 280 285

Cys Pro Thr Gly Ile Gln Leu Lys Gly Asp Gly Lys Thr Cys Asp Pro
290 295 300

Ser Pro Glu Thr Tyr Leu Leu Phe Ser Ser Arg Gly Ser Ile Arg Arg
305 310 315 320

Ile Ser Leu Asp Thr Ser Asp His Thr Asp Val His Val Pro Val Pro
325 330 335

Glu Leu Asn Asn Val Ile Ser Leu Asp Tyr Asp Ser Val Asp Gly Lys
340 345 350

Val Tyr Tyr Thr Asp Val Phe Leu Asp Val Ile Arg Arg Ala Asp Leu
355 360 365

Asn Gly Ser Asn Met Glu Thr Val Ile Gly Arg Gly Leu Lys Thr Thr
370 375 380

Asp Gly Leu Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp Thr Asp
385 390 395 400

Thr Gly Arg Asn Thr Ile Glu Ala Ser Arg Leu Asp Gly Ser Cys Arg
405 410 415

Lys Val Leu Ile Asn Asn Ser Leu Asp Glu Pro Arg Ala Ile Ala Val
420 425 430

Phe Pro Arg Lys Gly Tyr Leu Phe Trp Thr Asp Trp Gly His Ile Ala
435 440 445

Lys Ile Glu Arg Ala Asn Leu Asp Gly Ser Glu Arg Lys Val Leu Ile
450 455 460

Asn Thr Asp Leu Gly Trp Pro Asn Gly Leu Thr Leu Asp Tyr Asp Thr
465 470 475 480

Arg Arg Ile Tyr Trp Val Asp Ala His Leu Asp Arg Ile Glu Ser Ala
485 490 495

Asp Leu Asn Gly Lys Leu Arg Gln Val Leu Val Ser His Val Ser His
500 505 510

Pro Phe Ala Leu Thr Gln Gln Asp Arg Trp Ile Tyr Trp Thr Asp Trp
515 520 525

Gln Thr Lys Ser Ile Gln Arg Val Asp Lys Tyr Ser Gly Arg Asn Lys
530 535 540

Glu Thr Val Leu Ala Asn Val Glu Gly Leu Met Asp Ile Ile Val Val
545 550 555 560

Ser Pro Gln Arg Gln Thr Gly Thr Asn Ala Cys Gly Val Asn Asn Gly
565 570 575

Gly Cys Thr His Leu Cys Phe Ala Arg Ala Ser Asp Phe Val Cys Ala
580 585 590

Cys Pro Asp Glu Pro Asp Ser Arg Pro Cys Ser Leu Val Pro Gly Leu
595 600 605

Val Pro Pro Ala Pro Arg Ala Thr Gly Met Ser Glu Lys Ser Pro Val
610 615 620

Leu Pro Asn Thr Pro Pro Thr Thr Leu Tyr Ser Ser Thr Thr Arg Thr
625 630 635 640

Arg Thr Ser Leu Glu Glu Val Glu Gly Arg Cys Ser Glu Arg Asp Ala
645 650 655

Arg Leu Gly Leu Cys Ala Arg Ser Asn Asp Ala Val Pro Ala Ala Pro
660 665 670

Gly Glu Gly Leu His Ile Ser Tyr Ala Ile Gly Gly Leu Leu Ser Ile
675 680 685

Leu Leu Ile Leu Val Val Ile Ala Ala Leu Met Leu Tyr Arg His Lys
690 695 700

Lys Ser Lys Phe Thr Asp Pro Gly Met Gly Asn Leu Thr Tyr Ser Asn
705 710 715 720

Pro Ser Tyr Arg Thr Ser Thr Gln Glu Val Lys Ile Glu Ala Ile Pro
725 730 735

Lys Pro Ala Met Tyr Asn Gln Leu Cys Tyr Lys Lys Glu Gly Gly Pro
740 745 750

Asp His Asn Tyr Thr Lys Glu Lys Ile Lys Ile Val Glu Gly Ile Cys
755 760 765

Leu Leu Ser Gly Asp Asp Ala Glu Trp Asp Asp Leu Lys Gln Leu Arg
770 775 780

Ser Ser Arg Gly Gly Leu Leu Arg Asp His Val Cys Met Lys Thr Asp
785 790 795 800

Thr Val Ser Ile Gln Ala Ser Ser Gly Ser Leu Asp Asp Thr Glu Thr
805 810 815

Glu Gln Leu Leu Gln Glu Glu Gln Ser Glu Cys Ser Ser Val His Thr
820 825 830

Ala Ala Thr Pro Glu Arg Arg Gly Ser Leu Pro Asp Thr Gly Trp Lys
835 840 845

His Glu Arg Lys Leu Ser Ser Glu Ser Gln Val
850 855

<210> 80
<211> 1614
<212> PRT
<213> MOUSE

<400> 80

Met Glu Thr Ala Pro Thr Arg Ala Pro Pro Pro Pro Pro Pro Leu
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Leu Leu Leu Val Leu Tyr Cys Ser Leu Val Pro Ala Ala Ala Ser Pro
20 25 30

Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala Gly
35 40 45

Gly Val Lys Leu Glu Ser Thr Ile Val Ala Ser Gly Leu Glu Asp Ala
50 55 60

Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr Asp
65 70 75 80

Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly Ala
85 90 95

Ala Ala Gln Asn Ile Val Ile Ser Gly Leu Val Ser Pro Asp Gly Leu
100 105 110

Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu Thr

115 120 125

Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val Leu
130 135 140

Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro Ala
145 150 155 160

His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Ala Pro Arg Ile Glu
165 170 175

Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser Asp
180 185 190

Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys Leu
195 200 205

Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu Asp
210 215 220

Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro Phe
225 230 235 240

Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln Thr
245 250 255

Arg Ser Ile His Ala Cys Asn Lys Trp Thr Gly Glu Gln Arg Lys Glu
260 265 270

Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser Gln
275 280 285

Glu Arg Gln Pro Pro Phe His Thr Pro Cys Glu Glu Asp Asn Gly Gly
290 295 300

Cys Ser His Leu Cys Leu Leu Ser Pro Arg Glu Pro Phe Tyr Ser Cys
305 310 315 320

Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Lys Thr Cys Lys
325 330 335

Thr Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu Arg
340 345 350

Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln Val
355 360 365

Gly Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu Gly
370 375 380

Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala Tyr

385 390 395 400

Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn Asp
405 410 415

Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp Thr
420 425 430

Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr Ser
435 440 445

Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile Val
450 455 460

Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu Asn
465 470 475 480

Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Arg Asp Arg His Val Leu
485 490 495

Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu Gln
500 505 510

Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu Val
515 520 525

Ile Asn Ile Asp Gly Thr Lys Arg Lys Thr Leu Leu Glu Asp Lys Leu
530 535 540

Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp Thr
545 550 555 560

Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala Ser
565 570 575

Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys Ala
580 585 590

Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Gly Asn
595 600 605

Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro Arg Ala Thr Lys Cys
610 615 620

Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys Ile
625 630 635 640

Ile Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Thr Ile His Arg
645 650 655

Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr Gly

660 665 670

Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His Ile
675 680 685

Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met Asn
690 695 700

Gly Ser Ser Val Glu His Val Ile Glu Phe Gly Leu Asp Tyr Pro Glu
705 710 715 720

Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp Thr
725 730 735

Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg Gln
740 745 750

Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu Asp
755 760 765

Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro Arg
770 775 780

Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val Asp
785 790 795 800

Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln Arg
805 810 815

Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn Met
820 825 830

Leu Gly Gln Glu Arg Met Val Ile Ala Asp Asp Leu Pro Tyr Pro Phe
835 840 845

Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn Leu
850 855 860

His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr Leu
865 870 875 880

Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His Ser
885 890 895

Ser Arg Gln Asp Gly Leu Asn Asp Cys Val His Ser Asn Gly Gln Cys
900 905 910

Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys Ala
915 920 925

Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro Ser

930 935 940

Thr Phe Leu Leu Phe Ser Gln Lys Phe Ala Ile Ser Arg Met Ile Pro
945 950 955 960

Asp Asp Gln Leu Ser Pro Asp Leu Val Leu Pro Leu His Gly Leu Arg
965 970 975

Asn Val Lys Ala Ile Asn Tyr Asp Pro Leu Asp Lys Phe Ile Tyr Trp
980 985 990

Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr Gln
995 1000 1005

Pro Ser Met Leu Thr Ser Pro Ser Gln Ser Leu Ser Pro Asp Arg
1010 1015 1020

Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu Phe
1025 1030 1035

Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu Asp
1040 1045 1050

Gly Asp Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys Pro
1055 1060 1065

Arg Ala Ile Ala Val Asn Ala Glu Arg Gly Tyr Met Tyr Phe Thr
1070 1075 1080

Asn Met Gln Asp His Ala Ala Lys Ile Glu Arg Ala Ser Leu Asp
1085 1090 1095

Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg Pro
1100 1105 1110

Val Ala Leu Val Val Asp Asn Ala Leu Gly Lys Leu Phe Trp Val
1115 1120 1125

Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly Ala
1130 1135 1140

Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Val Gly
1145 1150 1155

Leu Thr Val Leu Gly Arg His Leu Tyr Trp Ile Asp Arg Gln Gln
1160 1165 1170

Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg Thr
1175 1180 1185

Arg Val Gln Gly Arg Val Thr His Leu Thr Gly Ile His Ala Val

1190 1195 1200

Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala Arg
1205 1210 1215

Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly Asp Gly
1220 1225 1230

Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln Asn
1235 1240 1245

Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln Phe
1250 1255 1260

Ala Cys Thr Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp Arg
1265 1270 1275

Cys Asp Gly Phe Pro Glu Cys Ala Asp Gln Ser Asp Glu Glu Gly
1280 1285 1290

Cys Pro Val Cys Ser Ala Ser Gln Phe Pro Cys Ala Arg Gly Gln
1295 1300 1305

Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys Gln
1310 1315 1320

Asp Arg Ser Asp Glu Ala Asn Cys Asp Ala Val Cys Leu Pro Asn
1325 1330 1335

Gln Phe Arg Cys Thr Ser Gly Gln Cys Val Leu Ile Lys Gln Gln
1340 1345 1350

Cys Asp Ser Phe Pro Asp Cys Ala Asp Gly Ser Asp Glu Leu Met
1355 1360 1365

Cys Glu Ile Asn Lys Pro Pro Ser Asp Asp Ile Pro Ala His Ser
1370 1375 1380

Ser Ala Ile Gly Pro Val Ile Gly Ile Ile Leu Ser Leu Phe Val
1385 1390 1395

Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Met Cys Gln Arg
1400 1405 1410

Tyr Thr Gly Ala Ser Gly Pro Phe Pro His Glu Tyr Val Gly Gly
1415 1420 1425

Ala Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser Gln
1430 1435 1440

His Gly Pro Phe Pro Gly Ile Pro Cys Ser Lys Ser Val Met Ser

1445 1450 1455

Ser Met Ser Leu Val Gly Gly Arg Gly Ser Val Pro Leu Tyr Asp
1460 1465 1470

Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser Thr
1475 1480 1485

Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser Pro
1490 1495 1500

Ala Thr Asp Pro Ser Leu Tyr Asn Val Asp Val Phe Tyr Ser Ser
1505 1510 1515

Gly Ile Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Val Ile Arg
1520 1525 1530

Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp
1535 1540 1545

Ser Asp Tyr Ser Ile Ser Arg Trp Lys Ser Ser Lys Tyr Tyr Leu
1550 1555 1560

Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro
1565 1570 1575

His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro
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Gly Thr Glu Arg Ser Tyr Cys His Leu Phe Pro Pro Pro Pro Ser
1595 1600 1605

Pro Cys Thr Asp Ser Ser
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<400> 81

Met Glu Ala Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu Leu Leu Leu
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Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser
20 25 30

Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala
35 40 45

Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp
50 55 60

Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr
65 70 75 80

Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly
85 90 95

Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly
100 105 110

Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu
115 120 125

Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val
130 135 140

Leu Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro
145 150 155 160

Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile
165 170 175

Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser
180 185 190

Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys
195 200 205

Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu
210 215 220

Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro
225 230 235 240

Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln
245 250 255

Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys
260 265 270

Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser
275 280 285

Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly
290 295 300

Gly Cys Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr
305 310 315 320

Cys Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Arg Thr Cys
325 330 335

Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu
340 345 350

Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln
355 360 365

Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu
370 375 380

Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala
385 390 395 400

Tyr Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn
405 410 415

Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp
420 425 430

Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr
435 440 445

Ser Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile
450 455 460

Ala Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu
465 470 475 480

Asn Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val
485 490 495

Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu
500 505 510

Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu
515 520 525

Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys
530 535 540

Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp
545 550 555 560

Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala
565 570 575

Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys
580 585 590

Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg
595 600 605

Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg
610 615 620

Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys
625 630 635 640

Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His
645 650 655

Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr
660 665 670

Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His
675 680 685

Ile Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met
690 695 700

Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro
705 710 715 720

Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp
725 730 735

Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg
740 745 750

Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu
755 760 765

Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro
770 775 780

Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val
785 790 795 800

Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln
805 810 815

Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn
820 825 830

Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro
835 840 845

Phe Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn
850 855 860

Leu His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr
865 870 875 880

Leu Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His
885 890 895

Ser Ser Arg Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln
900 905 910

Cys Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys
915 920 925

Ala Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro
930 935 940

Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile
945 950 955 960

Pro Asp Asp Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu
965 970 975

Arg Asn Val Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr
980 985 990

Trp Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr
995 1000 1005

Gln Pro Phe Val Leu Thr Ser Leu Ser Gln Gly Gln Asn Pro Asp
1010 1015 1020

Arg Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu
1025 1030 1035

Phe Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu
1040 1045 1050

Ser Gly Glu Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys
1055 1060 1065

Pro Arg Ala Ile Val Val Asn Ala Glu Arg Gly Tyr Leu Tyr Phe
1070 1075 1080

Thr Asn Met Gln Asp Arg Ala Ala Lys Ile Glu Arg Ala Ala Leu
1085 1090 1095

Asp Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg
1100 1105 1110

Pro Val Ala Leu Val Val Asp Asn Thr Leu Gly Lys Leu Phe Trp
1115 1120 1125

Val Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly
1130 1135 1140

Ala Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Leu
1145 1150 1155

Gly Leu Thr Ile Leu Gly Lys His Leu Tyr Trp Ile Asp Arg Gln
1160 1165 1170

Gln Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg
1175 1180 1185

Thr Arg Ile Gln Gly Arg Val Ala His Leu Thr Gly Ile His Ala
1190 1195 1200

Val Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala
1205 1210 1215

Arg Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly Asp
1220 1225 1230

Gly Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln
1235 1240 1245

Asn Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln
1250 1255 1260

Phe Ala Cys Ala Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp
1265 1270 1275

Arg Cys Asp Gly Phe Pro Glu Cys Asp Asp Gln Ser Asp Glu Glu
1280 1285 1290

Gly Cys Pro Val Cys Ser Ala Ala Gln Phe Pro Cys Ala Arg Gly
1295 1300 1305

Gln Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys
1310 1315 1320

Gln Asp Arg Ser Asp Glu Ala Asp Cys Asp Ala Ile Cys Leu Pro
1325 1330 1335

Asn Gln Phe Arg Cys Ala Ser Gly Gln Cys Val Leu Ile Lys Gln
1340 1345 1350

Gln Cys Asp Ser Phe Pro Asp Cys Ile Asp Gly Ser Asp Glu Leu
1355 1360 1365

Met Cys Glu Ile Thr Lys Pro Pro Ser Asp Asp Ser Pro Ala His
1370 1375 1380

Ser Ser Ala Ile Gly Pro Val Ile Gly Ile Ile Leu Ser Leu Phe
1385 1390 1395

Val Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Val Cys Gln
1400 1405 1410

Arg Tyr Ala Gly Ala Asn Gly Pro Phe Pro His Glu Tyr Val Ser
1415 1420 1425

Gly Thr Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser
1430 1435 1440

Gln His Gly Pro Phe Thr Gly Ile Ala Cys Gly Lys Ser Met Met
1445 1450 1455

Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly Val Pro Leu Tyr
1460 1465 1470

Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser
1475 1480 1485

Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser
1490 1495 1500

Pro Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr Ser
1505 1510 1515

Ser Asn Ile Pro Ala Thr Arg Pro Tyr Ile Ile Arg Gly Met Ala
1520 1525 1530

Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp Ser Asp Tyr
1535 1540 1545

Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr Leu Asp Leu Asn
1550 1555 1560

Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro His Ser Gln
1565 1570 1575

Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro Ala Thr Glu
1580 1585 1590

Arg Ser Tyr Phe His Leu Phe Pro Pro Pro Pro Ser Pro Cys Thr
1595 1600 1605

Asp Ser Ser
1610

<210> 82
<211> 1615
<212> PRT
<213> HOMO SAPIENS

<400> 82

Met Glu Ala Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser
20 25 30

Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala
35 40 45

Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp
50 55 60

Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr
65 70 75 80

Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly
85 90 95

Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly
100 105 110

Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu
115 120 125

Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val
130 135 140

Leu Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro
145 150 155 160

Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile
165 170 175

Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser
180 185 190

Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys
195 200 205

Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu
210 215 220

Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro
225 230 235 240

Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln
245 250 255

Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys
260 265 270

Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser
275 280 285

Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly
290 295 300

Gly Cys Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr
305 310 315 320

Cys Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Arg Thr Cys
325 330 335

Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu
340 345 350

Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln
355 360 365

Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu
370 375 380

Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala
385 390 395 400

Tyr Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn
405 410 415

Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp
420 425 430

Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr
435 440 445

Ser Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile
450 455 460

Ala Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu
465 470 475 480

Asn Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val
485 490 495

Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu
500 505 510

Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu
515 520 525

Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys
530 535 540

Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp
545 550 555 560

Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala
565 570 575

Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys
580 585 590

Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg
595 600 605

Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg
610 615 620

Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys
625 630 635 640

Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His
645 650 655

Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr
660 665 670

Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His
675 680 685

Ile Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met
690 695 700

Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro
705 710 715 720

Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp
725 730 735

Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg
740 745 750

Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu
755 760 765

Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro
770 775 780

Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val
785 790 795 800

Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln
805 810 815

Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn
820 825 830

Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro
835 840 845

Phe Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn
850 855 860

Leu His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr
865 870 875 880

Leu Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His
885 890 895

Ser Ser Arg Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln
900 905 910

Cys Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys
915 920 925

Ala Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro
930 935 940

Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile
945 950 955 960

Pro Asp Asp Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu
965 970 975

Arg Asn Val Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr
980 985 990

Trp Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr
995 1000 1005

Gln Pro Phe Val Leu Thr Ser Leu Ser Gln Gly Gln Asn Pro Asp
1010 1015 1020

Arg Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu
1025 1030 1035

Phe Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu
1040 1045 1050

Ser Gly Glu Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys
1055 1060 1065

Pro Arg Ala Ile Val Val Asn Ala Glu Arg Gly Tyr Leu Tyr Phe
1070 1075 1080

Thr Asn Met Gln Asp Arg Ala Ala Lys Ile Glu Arg Ala Ala Leu
1085 1090 1095

Asp Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg
1100 1105 1110

Pro Val Ala Leu Val Val Asp Asn Thr Leu Gly Lys Leu Phe Trp
1115 1120 1125

Val Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly
1130 1135 1140

Ala Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Leu
1145 1150 1155

Gly Leu Thr Ile Leu Gly Lys His Leu Tyr Trp Ile Asp Arg Gln
1160 1165 1170

Gln Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg
1175 1180 1185

Thr Arg Ile Gln Gly Arg Val Ala His Leu Thr Gly Ile His Ala
1190 1195 1200

Val Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala
1205 1210 1215

Arg Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly Asp
1220 1225 1230

Gly Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln
1235 1240 1245

Asn Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln
1250 1255 1260

Phe Ala Cys Ala Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp
1265 1270 1275

Arg Cys Asp Gly Phe Pro Glu Cys Asp Asp Gln Ser Asp Glu Glu
1280 1285 1290

Gly Cys Pro Val Cys Ser Ala Ala Gln Phe Pro Cys Ala Arg Gly
1295 1300 1305

Gln Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys
1310 1315 1320

Gln Asp Arg Ser Asp Glu Ala Asp Cys Asp Ala Ile Cys Leu Pro
1325 1330 1335

Asn Gln Phe Arg Cys Ala Ser Gly Gln Cys Val Leu Ile Lys Gln
1340 1345 1350

Gln Cys Asp Ser Phe Pro Asp Cys Ile Asp Gly Ser Asp Glu Leu
1355 1360 1365

Met Cys Glu Ile Thr Lys Pro Pro Ser Asp Asp Ser Pro Ala His
1370 1375 1380

Ser Ser Ala Ile Gly Pro Val Ile Gly Ile Ile Leu Ser Leu Phe
1385 1390 1395

Val Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Val Cys Gln
1400 1405 1410

Arg Tyr Ala Gly Ala Asn Gly Pro Phe Pro His Glu Tyr Val Ser
1415 1420 1425

Gly Thr Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser
1430 1435 1440

Gln His Gly Pro Phe Thr Gly Ile Ala Cys Gly Lys Ser Met Met
1445 1450 1455

Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly Val Pro Leu Tyr
1460 1465 1470

Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser
1475 1480 1485

Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser
1490 1495 1500

Pro Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr Ser
1505 1510 1515

Ser Asn Ile Pro Ala Thr Val Arg Pro Tyr Arg Pro Tyr Ile Ile
1520 1525 1530

Arg Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys
1535 1540 1545

Asp Ser Asp Tyr Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr
1550 1555 1560

Leu Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr
1565 1570 1575

Pro His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser
1580 1585 1590

Pro Ala Thr Glu Arg Ser Tyr Phe His Leu Phe Pro Pro Pro Pro
1595 1600 1605

Ser Pro Cys Thr Asp Ser Ser
1610 1615

<210> 83
<211> 1613
<212> PRT
<213> MOUSE

<400> 83

Met Gly Ala Val Leu Arg Ser Leu Leu Ala Cys Ser Phe Cys Val Leu
1 5 10 15

Leu Arg Ala Ala Pro Leu Leu Leu Tyr Ala Asn Arg Arg Asp Leu Arg
20 25 30

Leu Val Asp Ala Thr Asn Gly Lys Glu Asn Ala Thr Ile Val Val Gly
35 40 45

Gly Leu Glu Asp Ala Ala Ala Val Asp Phe Val Phe Gly His Gly Leu
50 55 60

Ile Tyr Trp Ser Asp Val Ser Glu Glu Ala Ile Lys Arg Thr Glu Phe
65 70 75 80

Asn Lys Ser Glu Ser Val Gln Asn Val Val Val Ser Gly Leu Leu Ser
85 90 95

Pro Asp Gly Leu Ala Cys Asp Trp Leu Gly Glu Lys Leu Tyr Trp Thr
100 105 110

Asp Ser Glu Thr Asn Arg Ile Glu Val Ser Asn Leu Asp Gly Ser Leu
115 120 125

Arg Lys Val Leu Phe Trp Gln Glu Leu Asp Gln Pro Arg Ala Ile Ala
130 135 140

Leu Asp Pro Ser Ser Gly Phe Met Tyr Trp Thr Asp Trp Gly Glu Val
145 150 155 160

Pro Lys Ile Glu Arg Ala Gly Met Asp Gly Ser Ser Arg Phe Val Ile
165 170 175

Ile Asn Thr Glu Ile Tyr Trp Pro Asn Gly Leu Thr Leu Asp Tyr Gln
180 185 190

Glu Arg Lys Leu Tyr Trp Ala Asp Ala Lys Leu Asn Phe Ile His Lys
195 200 205

Ser Asn Leu Asp Gly Thr Asn Arg Gln Ala Val Val Lys Gly Ser Leu
210 215 220

Pro His Pro Phe Ala Leu Thr Leu Phe Glu Asp Thr Leu Tyr Trp Thr
225 230 235 240

Asp Trp Asn Thr His Ser Ile Leu Ala Cys Asn Lys Tyr Thr Gly Glu
245 250 255

Gly Leu Arg Glu Ile His Ser Asn Ile Phe Ser Pro Met Asp Ile His
260 265 270

Ala Phe Ser Gln Gln Arg Gln Pro Asn Ala Thr Asn Pro Cys Gly Ile
275 280 285

Asp Asn Gly Gly Cys Ser His Leu Cys Leu Met Ser Pro Val Lys Pro
290 295 300

Phe Tyr Gln Cys Ala Cys Pro Thr Gly Val Lys Leu Met Glu Asn Gly
305 310 315 320

Lys Thr Cys Lys Asp Gly Ala Thr Glu Leu Leu Leu Leu Ala Arg Arg
325 330 335

Thr Asp Leu Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile
340 345 350

Val Leu Gln Leu Glu Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp
355 360 365

Pro Val Glu Gly Tyr Ile Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile
370 375 380

Arg Arg Ser Phe Ile Asp Gly Ser Gly Ser Gln Phe Val Val Thr Ala
385 390 395 400

Gln Ile Ala His Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn
405 410 415

Leu Tyr Trp Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu
420 425 430

Asn Gly Thr Met Arg Lys Ile Leu Ile Ser Glu Asp Leu Glu Glu Pro
435 440 445

Arg Ala Ile Val Leu Asp Pro Met Val Gly Tyr Met Tyr Trp Thr Asp
450 455 460

Trp Gly Glu Ile Pro Lys Ile Glu Arg Ala Ala Leu Asp Gly Ser Asp
465 470 475 480

Arg Val Val Leu Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala
485 490 495

Leu Asp Tyr Asp Glu Gly Thr Ile Tyr Trp Gly Asp Ala Lys Thr Asp
500 505 510

Lys Ile Glu Val Met Asn Thr Asp Gly Thr Gly Arg Arg Val Leu Val
515 520 525

Glu Asp Lys Ile Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Tyr
530 535 540

Val Tyr Trp Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys
545 550 555 560

Arg Ser Ala Glu Arg Glu Val Ile Ile Asp Gln Leu Pro Asp Leu Met
565 570 575

Gly Leu Lys Ala Thr Ser Val His Arg Val Ile Gly Ser Asn Pro Cys
580 585 590

Ala Glu Asp Asn Gly Gly Cys Ser His Leu Cys Leu Tyr Arg Pro Gln
595 600 605

Gly Leu Arg Cys Ala Cys Pro Ile Gly Phe Glu Leu Ile Gly Asp Met
610 615 620

Lys Thr Cys Ile Val Pro Glu Ala Phe Leu Leu Phe Ser Arg Arg Ala
625 630 635 640

Asp Ile Arg Arg Ile Ser Leu Glu Thr Asn Asn Asn Asn Val Ala Ile
645 650 655

Pro Leu Thr Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Thr
660 665 670

Asp Asn Arg Ile Tyr Trp Thr Asp Ile Ser Leu Lys Thr Ile Ser Arg
675 680 685

Ala Phe Met Asn Gly Ser Ala Leu Glu His Val Val Glu Phe Gly Leu
690 695 700

Asp Tyr Pro Glu Gly Met Ala Val Asp Trp Leu Gly Lys Asn Leu Tyr
705 710 715 720

Trp Ala Asp Thr Gly Thr Asn Arg Ile Glu Val Ser Lys Leu Asp Gly
725 730 735

Gln His Arg Gln Val Leu Val Trp Lys Asp Leu Asp Ser Pro Arg Ala
740 745 750

Leu Ala Leu Asp Pro Ala Glu Gly Phe Met Tyr Trp Thr Glu Trp Gly
755 760 765

Gly Lys Pro Lys Ile Asp Arg Ala Ala Met Asp Gly Ser Glu Arg Thr
770 775 780

Thr Leu Val Pro Asn Val Gly Arg Ala Asn Gly Leu Thr Ile Asp Tyr
785 790 795 800

Ala Lys Arg Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Leu Ile Glu
805 810 815

Ser Ser Asp Met Leu Gly Leu Asn Arg Glu Val Ile Ala Asp Asp Leu
820 825 830

Pro His Pro Phe Gly Leu Thr Gln Tyr Gln Asp Tyr Ile Tyr Trp Thr
835 840 845

Asp Trp Ser Arg Arg Ser Ile Glu Arg Ala Asn Lys Thr Ser Gly Gln
850 855 860

Asn Arg Thr Ile Ile Gln Gly His Leu Asp Tyr Val Met Asp Ile Leu
865 870 875 880

Val Phe His Ser Ser Arg Gln Ala Gly Trp Asn Glu Cys Ala Ser Ser
885 890 895

Asn Gly His Cys Ser His Leu Cys Leu Ala Val Pro Val Gly Gly Phe
900 905 910

Val Cys Gly Cys Pro Ala His Tyr Ser Leu Asn Ala Asp Asn Arg Thr
915 920 925

Cys Ser Ala Pro Ser Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile
930 935 940

Asn Arg Met Val Ile Asp Glu Gln Gln Ser Pro Asp Ile Ile Leu Pro
945 950 955 960

Ile His Ser Leu Arg Asn Val Arg Ala Ile Asp Tyr Asp Pro Leu Asp
965 970 975

Lys Gln Leu Tyr Trp Ile Asp Ser Arg Gln Asn Ser Ile Arg Lys Ala
980 985 990

His Glu Asp Gly Gly Gln Gly Phe Asn Val Val Ala Asn Ser Val Ala
995 1000 1005

Asn Gln Asn Leu Glu Ile Gln Pro Tyr Asp Leu Ser Ile Asp Ile
1010 1015 1020

Tyr Ser Arg Tyr Ile Tyr Trp Thr Cys Glu Ala Thr Asn Val Ile
1025 1030 1035

Asp Val Thr Arg Leu Asp Gly Arg Ser Val Gly Val Val Leu Lys
1040 1045 1050

Gly Glu Gln Asp Arg Pro Arg Ala Ile Val Val Asn Pro Glu Lys
1055 1060 1065

Gly Tyr Met Tyr Phe Thr Asn Leu Gln Glu Arg Ser Pro Lys Ile
1070 1075 1080

Glu Arg Ala Ala Leu Asp Gly Thr Glu Arg Glu Val Leu Phe Phe
1085 1090 1095

Ser Gly Leu Ser Lys Pro Ile Ala Leu Ala Leu Asp Ser Lys Leu
1100 1105 1110

Gly Lys Leu Phe Trp Ala Asp Ser Asp Leu Arg Arg Ile Glu Ser
1115 1120 1125

Ser Asp Leu Ser Gly Ala Asn Arg Ile Val Leu Glu Asp Ser Asn
1130 1135 1140

Ile Leu Gln Pro Val Gly Leu Thr Val Phe Glu Asn Trp Leu Tyr
1145 1150 1155

Trp Ile Asp Lys Gln Gln Gln Met Ile Glu Lys Ile Asp Met Thr
1160 1165 1170

Gly Arg Glu Gly Arg Thr Lys Val Gln Ala Arg Ile Ala Gln Leu
1175 1180 1185

Ser Asp Ile His Ala Val Lys Glu Leu Asn Leu Gln Glu Tyr Arg
1190 1195 1200

Gln His Pro Cys Ala Gln Asp Asn Gly Gly Cys Ser His Ile Cys
1205 1210 1215

Leu Val Lys Gly Asp Gly Thr Thr Arg Cys Ser Cys Pro Met His
1220 1225 1230

Leu Val Leu Leu Gln Asp Glu Leu Ser Cys Gly Glu Pro Pro Thr
1235 1240 1245

Cys Ser Pro Gln Gln Phe Thr Cys Phe Thr Gly Asp Ile Asp Cys
1250 1255 1260

Ile Pro Val Ala Trp Arg Cys Asp Gly Phe Thr Glu Cys Glu Asp
1265 1270 1275

His Ser Asp Glu Leu Asn Cys Pro Val Cys Ser Glu Ser Gln Phe
1280 1285 1290

Gln Cys Ala Ser Gly Gln Cys Ile Asp Gly Ala Leu Arg Cys Asn
1295 1300 1305

Gly Asp Ala Asn Cys Gln Asp Lys Ser Asp Glu Lys Asn Cys Glu
1310 1315 1320

Val Leu Cys Leu Ile Asp Gln Phe Arg Cys Ala Asn Gly Gln Cys
1325 1330 1335

Val Gly Lys His Lys Lys Cys Asp His Ser Val Asp Cys Ser Asp
1340 1345 1350

Arg Ser Asp Glu Leu Asp Cys Tyr Pro Thr Glu Glu Pro Ala Pro
1355 1360 1365

Gln Ala Thr Asn Thr Val Gly Ser Val Ile Gly Val Ile Val Thr
1370 1375 1380

Ile Phe Val Ser Gly Thr Ile Tyr Phe Ile Cys Gln Arg Met Leu
1385 1390 1395

Cys Pro Arg Met Lys Gly Asp Gly Glu Thr Met Thr Asn Asp Tyr
1400 1405 1410

Val Val His Ser Pro Ala Ser Val Pro Leu Gly Tyr Val Pro His
1415 1420 1425

Pro Ser Ser Leu Ser Gly Ser Leu Pro Gly Met Ser Arg Gly Lys
1430 1435 1440

Ser Met Ile Ser Ser Leu Ser Ile Met Gly Gly Ser Ser Gly Pro
1445 1450 1455

Pro Tyr Asp Arg Ala His Val Thr Gly Ala Ser Ser Ser Ser Ser
1460 1465 1470

Ser Ser Thr Lys Gly Thr Tyr Phe Pro Ala Ile Leu Asn Pro Pro
1475 1480 1485

Pro Ser Pro Ala Thr Glu Arg Ser His Tyr Thr Met Glu Phe Gly
1490 1495 1500

Tyr Ser Ser Asn Ser Pro Ser Thr His Arg Ser Tyr Ser Tyr Arg
1505 1510 1515

Pro Tyr Ser Tyr Arg His Phe Ala Pro Pro Thr Thr Pro Cys Ser
1520 1525 1530

Thr Asp Val Cys Asp Ser Asp Tyr Ala Pro Ser Arg Arg Met Thr
1535 1540 1545

Ser Val Ala Thr Ala Lys Gly Tyr Thr Ser Asp Val Asn Tyr Asp
1550 1555 1560

Ser Glu Pro Val Pro Pro Pro Pro Thr Pro Arg Ser Gln Tyr Leu
1565 1570 1575

Ser Ala Glu Glu Asn Tyr Glu Ser Cys Pro Pro Ser Pro Tyr Thr
1580 1585 1590

Glu Arg Ser Tyr Ser His His Leu Tyr Pro Pro Pro Pro Ser Pro
1595 1600 1605

Cys Thr Asp Ser Ser
1610

<210> 84
<211> 1613
<212> PRT
<213> HOMO SAPIENS

<400> 84

Met Gly Ala Val Leu Arg Ser Leu Leu Ala Cys Ser Phe Cys Val Leu
1 5 10 15

Leu Arg Ala Ala Pro Leu Leu Leu Tyr Ala Asn Arg Arg Asp Leu Arg
20 25 30

Leu Val Asp Ala Thr Asn Gly Lys Glu Asn Ala Thr Ile Val Val Gly
35 40 45

Gly Leu Glu Asp Ala Ala Ala Val Asp Phe Val Phe Ser His Gly Leu
50 55 60

Ile Tyr Trp Ser Asp Val Ser Glu Glu Ala Ile Lys Arg Thr Glu Phe
65 70 75 80

Asn Lys Thr Glu Ser Val Gln Asn Val Val Val Ser Gly Leu Leu Ser
85 90 95

Pro Asp Gly Leu Ala Cys Asp Trp Leu Gly Glu Lys Leu Tyr Trp Thr
100 105 110

Asp Ser Glu Thr Asn Arg Ile Glu Val Ser Asn Leu Asp Gly Ser Leu
115 120 125

Arg Lys Val Leu Phe Trp Gln Glu Leu Asp Gln Pro Arg Ala Ile Ala
130 135 140

Leu Asp Pro Ser Ser Gly Phe Met Tyr Trp Thr Asp Trp Gly Glu Val

145 150 155 160

Pro Lys Ile Glu Arg Ala Gly Met Asp Gly Ser Ser Arg Phe Ile Ile
165 170 175

Ile Asn Ser Glu Ile Tyr Trp Pro Asn Gly Leu Thr Leu Asp Tyr Glu
180 185 190

Glu Gln Lys Leu Tyr Trp Ala Asp Ala Lys Leu Asn Phe Ile His Lys
195 200 205

Ser Asn Leu Asp Gly Thr Asn Arg Gln Ala Val Val Lys Gly Ser Leu
210 215 220

Pro His Pro Phe Ala Leu Thr Leu Phe Glu Asp Ile Leu Tyr Trp Thr
225 230 235 240

Asp Trp Ser Thr His Ser Ile Leu Ala Cys Asn Lys Tyr Thr Gly Glu
245 250 255

Gly Leu Arg Glu Ile His Ser Asp Ile Phe Ser Pro Met Asp Ile His
260 265 270

Ala Phe Ser Gln Gln Arg Gln Pro Asn Ala Thr Asn Pro Cys Gly Ile
275 280 285

Asp Asn Gly Gly Cys Ser His Leu Cys Leu Met Ser Pro Val Lys Pro
290 295 300

Phe Tyr Gln Cys Ala Cys Pro Thr Gly Val Lys Leu Leu Glu Asn Gly
305 310 315 320

Lys Thr Cys Lys Asp Gly Ala Thr Glu Leu Leu Leu Leu Ala Arg Arg
325 330 335

Thr Asp Leu Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile
340 345 350

Val Leu Gln Leu Glu Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp
355 360 365

Pro Val Glu Gly Tyr Ile Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile
370 375 380

Arg Arg Ser Phe Ile Asp Gly Ser Gly Ser Gln Phe Val Val Thr Ala
385 390 395 400

Gln Ile Ala His Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn
405 410 415

Leu Tyr Trp Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu

420 425 430

Asn Gly Thr Met Arg Lys Ile Leu Ile Ser Glu Asp Leu Glu Glu Pro
435 440 445

Arg Ala Ile Val Leu Asp Pro Met Val Gly Tyr Met Tyr Trp Thr Asp
450 455 460

Trp Gly Glu Ile Pro Lys Ile Glu Arg Ala Ala Leu Asp Gly Ser Asp
465 470 475 480

Arg Val Val Leu Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala
485 490 495

Leu Asp Tyr Asp Glu Gly Lys Ile Tyr Trp Gly Asp Ala Lys Thr Asp
500 505 510

Lys Ile Glu Val Met Asn Thr Asp Gly Thr Gly Arg Arg Val Leu Val
515 520 525

Glu Asp Lys Ile Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Tyr
530 535 540

Val Tyr Trp Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys
545 550 555 560

Arg Ser Ala Glu Arg Glu Val Ile Ile Asp Gln Leu Pro Asp Leu Met
565 570 575

Gly Leu Lys Ala Thr Asn Val His Arg Val Ile Gly Ser Asn Pro Cys
580 585 590

Ala Glu Glu Asn Gly Gly Cys Ser His Leu Cys Leu Tyr Arg Pro Gln
595 600 605

Gly Leu Arg Cys Ala Cys Pro Ile Gly Phe Glu Leu Ile Ser Asp Met
610 615 620

Lys Thr Cys Ile Val Pro Glu Ala Phe Leu Leu Phe Ser Arg Arg Ala
625 630 635 640

Asp Ile Arg Arg Ile Ser Leu Glu Thr Asn Asn Asn Asn Val Ala Ile
645 650 655

Pro Leu Thr Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Thr
660 665 670

Asp Asn Arg Ile Tyr Trp Thr Asp Ile Ser Leu Lys Thr Ile Ser Arg
675 680 685

Ala Phe Met Asn Gly Ser Ala Leu Glu His Val Val Glu Phe Gly Leu

690 695 700

Asp Tyr Pro Glu Gly Met Ala Val Asp Trp Leu Gly Lys Asn Leu Tyr
705 710 715 720

Trp Ala Asp Thr Gly Thr Asn Arg Ile Glu Val Ser Lys Leu Asp Gly
725 730 735

Gln His Arg Gln Val Leu Val Trp Lys Asp Leu Asp Ser Pro Arg Ala
740 745 750

Leu Ala Leu Asp Pro Ala Glu Gly Phe Met Tyr Trp Thr Glu Trp Gly
755 760 765

Gly Lys Pro Lys Ile Asp Arg Ala Ala Met Asp Gly Ser Glu Arg Thr
770 775 780

Thr Leu Val Pro Asn Val Gly Arg Ala Asn Gly Leu Thr Ile Asp Tyr
785 790 795 800

Ala Lys Arg Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Leu Ile Glu
805 810 815

Ser Ser Asn Met Leu Gly Leu Asn Arg Glu Val Ile Ala Asp Asp Leu
820 825 830

Pro His Pro Phe Gly Leu Thr Gln Tyr Gln Asp Tyr Ile Tyr Trp Thr
835 840 845

Asp Trp Ser Arg Arg Ser Ile Glu Arg Ala Asn Lys Thr Ser Gly Gln
850 855 860

Asn Arg Thr Ile Ile Gln Gly His Leu Asp Tyr Val Met Asp Ile Leu
865 870 875 880

Val Phe His Ser Ser Arg Gln Ser Gly Trp Asn Glu Cys Ala Ser Ser
885 890 895

Asn Gly His Cys Ser His Leu Cys Leu Ala Val Pro Val Gly Gly Phe
900 905 910

Val Cys Gly Cys Pro Ala His Tyr Ser Leu Asn Ala Asp Asn Arg Thr
915 920 925

Cys Ser Ala Pro Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile
930 935 940

Asn Arg Met Val Ile Asp Glu Gln Gln Ser Pro Asp Ile Ile Leu Pro
945 950 955 960

Ile His Ser Leu Arg Asn Val Arg Ala Ile Asp Tyr Asp Pro Leu Asp

965 970 975

Lys Gln Leu Tyr Trp Ile Asp Ser Arg Gln Asn Met Ile Arg Lys Ala
980 985 990

Gln Glu Asp Gly Ser Gln Gly Phe Thr Val Val Val Ser Ser Val Pro
995 1000 1005

Ser Gln Asn Leu Glu Ile Gln Pro Tyr Asp Leu Ser Ile Asp Ile
1010 1015 1020

Tyr Ser Arg Tyr Ile Tyr Trp Thr Cys Glu Ala Thr Asn Val Ile
1025 1030 1035

Asn Val Thr Arg Leu Asp Gly Arg Ser Val Gly Val Val Leu Lys
1040 1045 1050

Gly Glu Gln Asp Arg Pro Arg Ala Ile Val Val Asn Pro Glu Lys
1055 1060 1065

Gly Tyr Met Tyr Phe Thr Asn Leu Gln Glu Arg Ser Pro Lys Ile
1070 1075 1080

Glu Arg Ala Ala Leu Asp Gly Thr Glu Arg Glu Val Leu Phe Phe
1085 1090 1095

Ser Gly Leu Ser Lys Pro Ile Ala Leu Ala Leu Asp Ser Arg Leu
1100 1105 1110

Gly Lys Leu Phe Trp Ala Asp Ser Asp Leu Arg Arg Ile Glu Ser
1115 1120 1125

Ser Asp Leu Ser Gly Ala Asn Arg Ile Val Leu Glu Asp Ser Asn
1130 1135 1140

Ile Leu Gln Pro Val Gly Leu Thr Val Phe Glu Asn Trp Leu Tyr
1145 1150 1155

Trp Ile Asp Lys Gln Gln Gln Met Ile Glu Lys Ile Asp Met Thr
1160 1165 1170

Gly Arg Glu Gly Arg Thr Lys Val Gln Ala Arg Ile Ala Gln Leu
1175 1180 1185

Ser Asp Ile His Ala Val Lys Glu Leu Asn Leu Gln Glu Tyr Arg
1190 1195 1200

Gln His Pro Cys Ala Gln Asp Asn Gly Gly Cys Ser His Ile Cys
1205 1210 1215

Leu Val Lys Gly Asp Gly Thr Thr Arg Cys Ser Cys Pro Met His

1220 1225 1230

Leu Val Leu Leu Gln Asp Glu Leu Ser Cys Gly Glu Pro Pro Thr
1235 1240 1245

Cys Ser Pro Gln Gln Phe Thr Cys Phe Thr Gly Glu Ile Asp Cys
1250 1255 1260

Ile Pro Val Ala Trp Arg Cys Asp Gly Phe Thr Glu Cys Glu Asp
1265 1270 1275

His Ser Asp Glu Leu Asn Cys Pro Val Cys Ser Glu Ser Gln Phe
1280 1285 1290

Gln Cys Ala Ser Gly Gln Cys Ile Asp Gly Ala Leu Arg Cys Asn
1295 1300 1305

Gly Asp Ala Asn Cys Gln Asp Lys Ser Asp Glu Lys Asn Cys Glu
1310 1315 1320

Val Leu Cys Leu Ile Asp Gln Phe Arg Cys Ala Asn Gly Gln Cys
1325 1330 1335

Ile Gly Lys His Lys Lys Cys Asp His Asn Val Asp Cys Ser Asp
1340 1345 1350

Lys Ser Asp Glu Leu Asp Cys Tyr Pro Thr Glu Glu Pro Ala Pro
1355 1360 1365

Gln Ala Thr Asn Thr Val Gly Ser Val Ile Gly Val Ile Val Thr
1370 1375 1380

Ile Phe Val Ser Gly Thr Val Tyr Phe Ile Cys Gln Arg Met Leu
1385 1390 1395

Cys Pro Arg Met Lys Gly Asp Gly Glu Thr Met Thr Asn Asp Tyr
1400 1405 1410

Val Val His Gly Pro Ala Ser Val Pro Leu Gly Tyr Val Pro His
1415 1420 1425

Pro Ser Ser Leu Ser Gly Ser Leu Pro Gly Met Ser Arg Gly Lys
1430 1435 1440

Ser Met Ile Ser Ser Leu Ser Ile Met Gly Gly Ser Ser Gly Pro
1445 1450 1455

Pro Tyr Asp Arg Ala His Val Thr Gly Ala Ser Ser Ser Ser Ser
1460 1465 1470

Ser Ser Thr Lys Gly Thr Tyr Phe Pro Ala Ile Leu Asn Pro Pro

1475 1480 1485

Pro Ser Pro Ala Thr Glu Arg Ser His Tyr Thr Met Glu Phe Gly
1490 1495 1500

Tyr Ser Ser Asn Ser Pro Ser Thr His Arg Ser Tyr Ser Tyr Arg
1505 1510 1515

Pro Tyr Ser Tyr Arg His Phe Ala Pro Pro Thr Thr Pro Cys Ser
1520 1525 1530

Thr Asp Val Cys Asp Ser Asp Tyr Ala Pro Ser Arg Arg Met Thr
1535 1540 1545

Ser Val Ala Thr Ala Lys Gly Tyr Thr Ser Asp Leu Asn Tyr Asp
1550 1555 1560

Ser Glu Pro Val Pro Pro Pro Pro Thr Pro Arg Ser Gln Tyr Leu
1565 1570 1575

Ser Ala Glu Glu Asn Tyr Glu Ser Cys Pro Pro Ser Pro Tyr Thr
1580 1585 1590

Glu Arg Ser Tyr Ser His His Leu Tyr Pro Pro Pro Pro Ser Pro
1595 1600 1605

Cys Thr Asp Ser Ser
1610

<210> 85
<211> 996
<212> PRT
<213> MOUSE

<400> 85

Met Gly Arg Pro Glu Leu Gly Ala Leu Arg Pro Leu Ala Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Gln Leu Gln His Leu Ser Ala Ala Asp Pro Leu Leu
20 25 30

Gly Gly Gln Gly Pro Val Lys Glu Cys Glu Glu Asp Gln Phe Arg Cys
35 40 45

Arg Asn Glu Arg Cys Ile Pro Leu Val Trp Arg Cys Asp Glu Asp Asn
50 55 60

Asp Cys Ser Asp Asn Ser Asp Glu Asp Asp Cys Pro Lys Arg Thr Cys
65 70 75 80

Ala Asp Ser Asp Phe Thr Cys Asp Asn Gly His Cys Ile Pro Glu Arg
85 90 95

Trp Lys Cys Asp Gly Glu Glu Glu Cys Pro Asp Gly Ser Asp Glu Ser
100 105 110

Lys Ala Thr Cys Ser Ser Glu Glu Cys Pro Ala Glu Lys Leu Ser Cys
115 120 125

Gly Pro Thr Ser His Lys Cys Val Pro Ala Ser Trp Arg Cys Asp Gly
130 135 140

Glu Lys Asp Cys Glu Gly Gly Ala Asp Glu Ala Gly Cys Pro Thr Leu
145 150 155 160

Cys Ala Pro His Glu Phe Gln Cys Ser Asn Arg Ser Cys Leu Ala Ser
165 170 175

Val Phe Val Cys Asp Gly Asp Asp Asp Cys Gly Asp Gly Ser Asp Glu
180 185 190

Arg Gly Cys Ser Asp Pro Ala Cys Pro Pro Arg Glu Phe Arg Cys Gly
195 200 205

Gly Gly Gly Thr Cys Ile Pro Glu Arg Trp Val Cys Asp Arg Gln Phe
210 215 220

Asp Cys Glu Asp Arg Ser Asp Glu Ala Ala Glu Leu Cys Gly Arg Ala
225 230 235 240

Gly Gln Gly Thr Thr Ala Thr Pro Ala Ala Cys Ala Pro Thr Ala Gln
245 250 255

Phe Thr Cys Arg Ser Gly Glu Cys Ile His Leu Gly Trp Arg Cys Asp
260 265 270

Gly Asp Arg Asp Cys Lys Asp Lys Ser Asp Glu Ala Asp Cys Ser Pro
275 280 285

Gly Pro Cys Arg Glu Asn Glu Phe Gln Cys Gly Asp Gly Thr Cys Val
290 295 300

Leu Ala Ile Lys Arg Cys Asn Gln Glu Arg Asp Cys Pro Asp Gly Ser
305 310 315 320

Asp Glu Ala Gly Cys Leu Gln Glu Ser Thr Cys Glu Gly Pro Arg Arg
325 330 335

Phe Gln Cys Lys Ser Gly Glu Cys Val Asp Gly Gly Lys Val Cys Asp
340 345 350

Asp Gln Arg Asp Cys Arg Asp Trp Ser Asp Glu Pro Gln Lys Val Cys
355 360 365

Gly Leu Asn Glu Cys Leu His Asn Asn Gly Gly Cys Ser His Ile Cys
370 375 380

Thr Asp Leu Lys Ile Gly Phe Glu Cys Thr Cys Pro Ala Gly Phe Gln
385 390 395 400

Leu Leu Asp Gln Lys Thr Cys Gly Asp Ile Asp Glu Cys Gln Asp Pro
405 410 415

Asp Ala Cys Ser Gln Ile Cys Val Asn Tyr Lys Gly Tyr Phe Lys Cys
420 425 430

Glu Cys His Pro Gly Tyr Glu Met Asp Thr Leu Thr Lys Asn Cys Lys
435 440 445

Ala Val Ala Gly Lys Ser Pro Ser Leu Ile Phe Thr Asn Arg His Glu
450 455 460

Val Arg Arg Ile Asp Leu Val Lys Arg Asp Tyr Ser Arg Leu Ile Pro
465 470 475 480

Met Leu Lys Asn Val Val Ala Leu Asp Val Glu Val Ala Thr Asn Arg
485 490 495

Ile Tyr Trp Cys Asp Leu Ser Tyr Arg Lys Ile Tyr Ser Ala His Met
500 505 510

Asp Lys Ala Ser Ile Pro Asp Glu Gln Val Val Leu Ile Asp Glu Gln
515 520 525

Leu His Ser Pro Glu Gly Leu Ala Val Asp Trp Val His Lys His Ile
530 535 540

Tyr Trp Thr Asp Ser Gly Asn Lys Thr Ile Ser Val Ala Thr Thr Asp
545 550 555 560

Gly Arg Arg Arg Cys Thr Leu Phe Ser Arg Glu Leu Ser Glu Pro Arg
565 570 575

Ala Ile Ala Val Asp Pro Leu Arg Gly Phe Met Tyr Trp Ser Asp Trp
580 585 590

Gly Phe Gln Ala Lys Ile Glu Lys Ala Gly Leu Asn Gly Ala Asp Arg
595 600 605

Gln Thr Leu Val Ser Asp Asn Ile Glu Trp Pro Asn Gly Ile Thr Leu
610 615 620

Asp Leu Leu Ser Gln Arg Leu Tyr Trp Val Asp Ser Lys Leu His Gln
625 630 635 640

Leu Ser Ser Ile Asp Phe Asn Gly Gly Asn Arg Lys Met Leu Ile Phe
645 650 655

Ser Thr Asp Phe Leu Ser His Pro Phe Gly Val Ala Val Phe Glu Asp
660 665 670

Lys Val Phe Trp Thr Asp Leu Glu Asn Glu Ala Ile Phe Ser Ala Asn
675 680 685

Arg Leu Asn Gly Leu Glu Ile Ala Ile Leu Ala Glu Asn Leu Asn Asn
690 695 700

Pro His Asp Ile Val Ile Phe His Glu Leu Lys Gln Pro Lys Ala Ala
705 710 715 720

Asp Ala Cys Asp Leu Ser Ala Gln Pro Asn Gly Gly Cys Glu Tyr Leu
725 730 735

Cys Leu Pro Ala Pro Gln Ile Ser Ser His Ser Pro Lys Tyr Thr Cys
740 745 750

Ala Cys Pro Asp Thr Met Trp Leu Gly Pro Asp Met Lys Arg Cys Tyr
755 760 765

Arg Ala Pro Gln Ser Thr Ser Thr Thr Thr Leu Ala Ser Ala Met Thr
770 775 780

Arg Thr Val Pro Ala Thr Thr Arg Ala Pro Gly Thr Thr Ile His Asp
785 790 795 800

Pro Thr Tyr Gln Asn His Ser Thr Glu Thr Pro Ser Gln Thr Ala Ala
805 810 815

Ala Pro His Ser Val Asn Val Pro Arg Ala Pro Ser Thr Ser Pro Ser
820 825 830

Thr Pro Ser Pro Ala Thr Ser Asn His Ser Gln His Tyr Gly Asn Glu
835 840 845

Gly Ser Gln Met Gly Ser Thr Val Thr Ala Ala Val Ile Gly Val Ile
850 855 860

Val Pro Ile Val Val Ile Ala Leu Leu Cys Met Ser Gly Tyr Leu Ile
865 870 875 880

Trp Arg Asn Trp Lys Arg Lys Asn Thr Lys Ser Met Asn Phe Asp Asn
885 890 895

Pro Val Tyr Arg Lys Thr Thr Glu Glu Glu Glu Glu Asp Glu Leu His
900 905 910

Ile Gly Arg Thr Ala Gln Ile Gly His Val Tyr Pro Ala Ala Ile Ser
915 920 925

Asn Tyr Asp Arg Pro Leu Trp Ala Glu Pro Cys Leu Gly Glu Thr Arg
930 935 940

Asp Leu Glu Asp Pro Ala Pro Ala Leu Lys Glu Leu Phe Val Leu Pro
945 950 955 960

Gly Glu Pro Arg Ser Gln Leu His Gln Leu Pro Lys Asn Pro Leu Ser
965 970 975

Glu Leu Pro Val Val Lys Cys Lys Arg Val Ala Leu Ser Leu Glu Asp
980 985 990

Asp Gly Leu Pro
995

<210> 86
<211> 963
<212> PRT
<213> HOMO SAPIENS

<400> 86

Met Gly Leu Pro Glu Pro Gly Pro Leu Arg Leu Leu Ala Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Leu Leu Leu Leu Arg Leu Gln His Leu Ala Ala Ala
20 25 30

Ala Ala Asp Pro Leu Leu Gly Gly Gln Gly Pro Ala Lys Glu Cys Glu
35 40 45

Lys Asp Gln Phe Gln Cys Arg Asn Glu Arg Cys Ile Pro Ser Val Trp
50 55 60

Arg Cys Asp Glu Asp Asp Asp Cys Leu Asp His Ser Asp Glu Asp Asp
65 70 75 80

Cys Pro Lys Lys Thr Cys Ala Asp Ser Asp Phe Thr Cys Asp Asn Gly
85 90 95

His Cys Ile His Glu Arg Trp Lys Cys Asp Gly Glu Glu Glu Cys Pro
100 105 110

Asp Gly Ser Asp Glu Ser Glu Ala Thr Cys Thr Lys Gln Val Cys Pro
115 120 125

Ala Glu Lys Leu Ser Cys Gly Pro Thr Ser His Lys Cys Val Pro Ala
130 135 140

Ser Trp Arg Cys Asp Gly Glu Lys Asp Cys Glu Gly Gly Ala Asp Glu
145 150 155 160

Ala Gly Cys Ala Thr Leu Cys Ala Pro His Glu Phe Gln Cys Gly Asn
165 170 175

Arg Ser Cys Leu Ala Ala Val Phe Val Cys Asp Gly Asp Asp Asp Cys
180 185 190

Gly Asp Gly Ser Asp Glu Arg Gly Cys Ala Asp Pro Ala Cys Gly Pro
195 200 205

Arg Glu Phe Arg Cys Gly Gly Asp Gly Gly Gly Ala Cys Ile Pro Glu
210 215 220

Arg Trp Val Cys Asp Arg Gln Phe Asp Cys Glu Asp Arg Ser Asp Glu
225 230 235 240

Ala Ala Glu Leu Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala Pro
245 250 255

Ala Ala Cys Ala Thr Val Ser Gln Phe Ala Cys Arg Ser Gly Glu Cys
260 265 270

Val His Leu Gly Trp Arg Cys Asp Gly Asp Arg Asp Cys Lys Asp Lys
275 280 285

Ser Asp Glu Ala Asp Cys Pro Leu Gly Thr Cys Arg Gly Asp Glu Phe
290 295 300

Gln Cys Gly Asp Gly Thr Cys Val Leu Ala Ile Lys His Cys Asn Gln
305 310 315 320

Glu Gln Asp Cys Pro Asp Gly Ser Asp Glu Ala Gly Cys Leu Gln Gly
325 330 335

Leu Asn Glu Cys Leu His Asn Asn Gly Gly Cys Ser His Ile Cys Thr
340 345 350

Asp Leu Lys Ile Gly Phe Glu Cys Thr Cys Pro Ala Gly Phe Gln Leu
355 360 365

Leu Asp Gln Lys Thr Cys Gly Asp Ile Asp Glu Cys Lys Asp Pro Asp
370 375 380

Ala Cys Ser Gln Ile Cys Val Asn Tyr Lys Gly Tyr Phe Lys Cys Glu
385 390 395 400

Cys Tyr Pro Gly Tyr Glu Met Asp Leu Leu Thr Lys Asn Cys Lys Ala
405 410 415

Ala Gly Gly Lys Ser Pro Ser Leu Ile Phe Thr Asn Arg Tyr Glu Val
420 425 430

Arg Arg Ile Asp Leu Val Lys Arg Asn Tyr Ser Arg Leu Ile Pro Met
435 440 445

Leu Lys Asn Val Val Ala Leu Asp Val Glu Val Ala Thr Asn Arg Ile
450 455 460

Tyr Trp Cys Asp Leu Ser Tyr Arg Lys Ile Tyr Ser Ala Tyr Met Asp
465 470 475 480

Lys Ala Ser Asp Pro Lys Glu Gln Glu Val Leu Ile Asp Glu Gln Leu
485 490 495

His Ser Pro Glu Gly Leu Ala Val Asp Trp Val His Lys His Ile Tyr
500 505 510

Trp Thr Asp Ser Gly Asn Lys Thr Ile Ser Val Ala Thr Val Asp Gly
515 520 525

Gly Arg Arg Arg Thr Leu Phe Ser Arg Asn Leu Ser Glu Pro Arg Ala
530 535 540

Ile Ala Val Asp Pro Leu Arg Gly Phe Met Tyr Trp Ser Asp Trp Gly
545 550 555 560

Asp Gln Ala Lys Ile Glu Lys Ser Gly Leu Asn Gly Val Asp Arg Gln
565 570 575

Thr Leu Val Ser Asp Asn Ile Glu Trp Pro Asn Gly Ile Thr Leu Asp
580 585 590

Leu Leu Ser Gln Arg Leu Tyr Trp Val Asp Ser Lys Leu His Gln Leu
595 600 605

Ser Ser Ile Asp Phe Ser Gly Gly Asn Arg Lys Thr Leu Ile Ser Ser
610 615 620

Thr Asp Phe Leu Ser His Pro Phe Gly Ile Ala Val Phe Glu Asp Lys
625 630 635 640

Val Phe Trp Thr Asp Leu Glu Asn Glu Ala Ile Phe Ser Ala Asn Arg
645 650 655

Leu Asn Gly Leu Glu Ile Ser Ile Leu Ala Glu Asn Leu Asn Asn Pro
660 665 670

His Asp Ile Val Ile Phe His Glu Leu Lys Gln Pro Arg Ala Pro Asp
675 680 685

Ala Cys Glu Leu Ser Val Gln Pro Asn Gly Gly Cys Glu Tyr Leu Cys
690 695 700

Leu Pro Ala Pro Gln Ile Ser Ser His Ser Pro Lys Tyr Thr Cys Ala
705 710 715 720

Cys Pro Asp Thr Met Trp Leu Gly Pro Asp Met Lys Arg Cys Tyr Arg
725 730 735

Ala Pro Gln Ser Thr Ser Thr Thr Thr Leu Ala Ser Thr Met Thr Arg
740 745 750

Thr Val Pro Ala Thr Thr Arg Ala Pro Gly Thr Thr Val His Arg Ser
755 760 765

Thr Tyr Gln Asn His Ser Thr Glu Thr Pro Ser Leu Thr Ala Ala Val
770 775 780

Pro Ser Ser Val Ser Val Pro Arg Ala Pro Ser Ile Ser Pro Ser Thr
785 790 795 800

Leu Ser Pro Ala Thr Ser Asn His Ser Gln His Tyr Ala Asn Glu Asp
805 810 815

Ser Lys Met Gly Ser Thr Val Thr Ala Ala Val Ile Gly Ile Ile Val
820 825 830

Pro Ile Val Val Ile Ala Leu Leu Cys Met Ser Gly Tyr Leu Ile Trp
835 840 845

Arg Asn Trp Lys Arg Lys Asn Thr Lys Ser Met Asn Phe Asp Asn Pro
850 855 860

Val Tyr Arg Lys Thr Thr Glu Glu Glu Asp Glu Asp Glu Leu His Ile
865 870 875 880

Gly Arg Thr Ala Gln Ile Gly His Val Tyr Pro Ala Ala Ile Ser Ser
885 890 895

Phe Asp Arg Pro Leu Trp Ala Glu Pro Cys Leu Gly Glu Thr Arg Glu
900 905 910

Pro Glu Asp Pro Ala Pro Ala Leu Lys Glu Leu Phe Val Leu Pro Gly
915 920 925

Glu Pro Arg Ser Gln Leu His Gln Leu Pro Lys Asn Pro Leu Ser Glu
930 935 940

Leu Pro Val Val Lys Ser Lys Arg Val Ala Leu Ser Leu Glu Asp Asp
945 950 955 960

Gly Leu Pro

<210> 87
<211> 713
<212> PRT
<213> MOUSE

<400> 87

Met Leu Ser Ala Leu Pro Leu Leu Phe Leu Leu Leu Gly Gly Ala Leu
1 5 10 15

Ala Arg Pro Asp Arg Ile Thr Phe Pro Arg Ser Ala Cys Glu Ala Pro
20 25 30

Pro Ala Val Leu Ser Glu Val Gln Gly Thr Leu Gln Arg Pro Leu Gly
35 40 45

Arg Asp Ser Arg Ser Ser Pro Ala Asn Cys Thr Trp Val Ile Leu Gly
50 55 60

Ser Lys Asp Gln Thr Val Thr Val Arg Phe Gln Lys Leu His Leu Ala
65 70 75 80

Cys Gly Ser Glu His Leu Ile Leu His Ser Pro Leu Gln Pro Pro Ile
85 90 95

Ser Leu Cys Glu Ala Pro Ser Gly Pro Leu Gln Leu Pro Gly Gly Asn
100 105 110

Val Thr Ile Thr Tyr Ser Tyr Ala Gly Ala Arg Ala Pro Met Gly Gln
115 120 125

Gly Phe Leu Leu Thr Tyr Ser Gln Asp Trp Leu Leu Cys Leu Gln Glu
130 135 140

Glu Phe Gln Cys Leu Asn His Arg Cys Ile Pro Ala Ala Gln Arg Cys
145 150 155 160

Asp Gly Ile Asp Ala Cys Gly Asp Gly Ser Asp Glu Ala Gly Cys Ser
165 170 175

Ser Asp Pro Phe Pro Asn Leu Asn Pro Ala Pro Ala Pro Thr Leu Ala
180 185 190

Cys Asn Leu Thr Leu Glu Asp Phe Tyr Gly Val Phe Ser Ser Pro Gly
195 200 205

Tyr Ser His Leu Ala Ser Val Ser His Pro Gln Ser Cys Leu Trp Leu
210 215 220

Leu Asp Pro His Asp Gly Arg Arg Leu Ala Val Arg Phe Thr Ala Leu
225 230 235 240

Asp Leu Ser Tyr Gly Asp Ala Val His Val Tyr Asp Gly Ala Gly Pro
245 250 255

Pro Glu Thr Pro Arg Leu Leu Arg Ser Leu Thr His Phe Ser Asn Gly
260 265 270

Lys Ala Val Thr Val Glu Thr Leu Ser Gly Gln Ala Val Val Ser Tyr
275 280 285

His Thr Val Ala Trp Ser Ser Gly Arg Gly Phe Asn Ala Thr Tyr His
290 295 300

Val Arg Gly Tyr Cys Leu Pro Trp Asp Arg Pro Cys Gly Leu Gly Ser
305 310 315 320

Gly Leu Gly Ala Ser Glu Asn Leu Gly Glu Arg Cys Tyr Ser Glu Ala
325 330 335

Gln Arg Cys Asp Gly Ser Trp Asp Cys Ala Asp Gly Thr Asp Glu Glu
340 345 350

Gly Cys Pro Gly Cys Pro Pro Gly His Phe Pro Cys Gly Ala Ala Gly
355 360 365

Thr Pro Gly Ala Thr Ala Cys Tyr Leu Pro Ala Asp Arg Cys Asn Tyr
370 375 380

Gln Thr Phe Cys Ala Asp Gly Ala Asp Glu Arg Arg Cys Arg His Cys
385 390 395 400

Gln Pro Gly Asn Phe Arg Cys Arg Asp Glu Lys Cys Val Tyr Glu Thr
405 410 415

Trp Val Cys Asp Gly Gln Pro Asp Cys Thr Asp Gly Ser Asp Glu Trp
420 425 430

Asp Cys Ser Tyr Ala Leu Pro Arg Lys Val Ile Thr Ala Ala Val Ile
435 440 445

Gly Ser Leu Val Cys Gly Leu Leu Leu Val Ile Ala Leu Gly Cys Thr
450 455 460

Cys Lys Leu Tyr Ala Ile Arg Thr Gln Glu Tyr Ser Ile Phe Ala Pro
465 470 475 480

Leu Ser Arg Met Glu Ala Glu Ile Val Gln Gln Gln Ala Pro Pro Ser
485 490 495

Tyr Gly Gln Leu Ile Ala Gln Gly Ala Ile Pro Pro Val Glu Asp Phe
500 505 510

Pro Thr Glu Asn Pro Asn Asp Asn Ser Val Leu Gly Asn Leu Arg Ser
515 520 525

Leu Leu Gln Ile Leu Arg Gln Asp Met Thr Pro Gly Gly Thr Ser Gly
530 535 540

Gly Arg Arg Arg Gln Arg Gly Arg Ser Val Arg Arg Leu Val Arg Arg
545 550 555 560

Leu Arg Arg Trp Gly Leu Leu Pro Arg Thr Asn Thr Pro Ala Arg Ala
565 570 575

Pro Glu Thr Arg Ser Gln Val Thr Pro Ser Val Pro Ser Glu Ala Leu
580 585 590

Asp Asp Ser Thr Gly His Ala Cys Glu Gly Gly Ala Val Gly Gly Gln
595 600 605

Asp Gly Glu Gln Ala Pro Pro Leu Pro Ile Lys Thr Pro Ile Pro Thr
610 615 620

Pro Ser Thr Leu Pro Ala Leu Ala Thr Val Ser Glu Thr Pro Gly Pro
625 630 635 640

Leu Pro Ser Val Pro Val Glu Ser Ser Leu Leu Ser Gly Val Val Gln
645 650 655

Val Leu Arg Gly Arg Leu Leu Pro Ser Leu Trp Ser Pro Gly Pro Thr
660 665 670

Trp Thr Gln Thr Gly Thr His Thr Thr Val Leu Ser Pro Glu Asp Glu
675 680 685

Asp Asp Val Leu Leu Leu Pro Leu Ala Glu Pro Glu Val Trp Val Val
690 695 700

Glu Ala Glu Asp Glu Pro Leu Leu Ala
705 710

<210> 88
<211> 713
<212> PRT
<213> MOUSE

<400> 88

Met Leu Ser Ala Leu Pro Leu Leu Phe Leu Leu Leu Gly Gly Ala Leu
1 5 10 15

Ala Arg Pro Asp Arg Ile Thr Phe Pro Arg Ser Ala Cys Glu Ala Pro

20 25 30

Pro Ala Val Leu Ser Glu Val Gln Gly Thr Leu Gln Arg Pro Leu Gly
35 40 45

Arg Asp Ser Arg Ser Ser Pro Ala Asn Cys Thr Trp Val Ile Leu Gly
50 55 60

Ser Lys Asp Gln Thr Val Thr Val Arg Phe Gln Lys Leu His Leu Ala
65 70 75 80

Cys Gly Ser Glu His Leu Ile Leu His Ser Pro Leu Gln Pro Pro Ile
85 90 95

Ser Leu Cys Glu Ala Pro Ser Gly Pro Leu Gln Leu Pro Gly Gly Asn
100 105 110

Val Thr Ile Thr Tyr Ser Tyr Ala Gly Ala Arg Ala Pro Met Gly Gln
115 120 125

Gly Phe Leu Leu Thr Tyr Ser Gln Asp Trp Leu Leu Cys Leu Gln Glu
130 135 140

Glu Phe Gln Cys Leu Asn His Arg Cys Ile Pro Ala Ala Gln Arg Cys
145 150 155 160

Asp Gly Ile Asp Ala Cys Gly Asp Gly Ser Asp Glu Ala Gly Cys Ser
165 170 175

Ser Asp Pro Phe Pro Asn Leu Asn Pro Ala Pro Ala Pro Thr Leu Ala
180 185 190

Cys Asn Leu Thr Leu Glu Asp Phe Tyr Gly Val Phe Ser Ser Pro Gly
195 200 205

Tyr Ser His Leu Ala Ser Val Ser His Pro Gln Ser Cys Leu Trp Leu
210 215 220

Leu Asp Pro His Asp Gly Arg Arg Leu Ala Val Arg Phe Thr Ala Leu
225 230 235 240

Asp Leu Ser Tyr Gly Asp Ala Val His Val Tyr Asp Gly Ala Gly Pro
245 250 255

Pro Glu Thr Pro Arg Leu Leu Arg Ser Leu Thr His Phe Ser Asn Gly
260 265 270

Lys Ala Val Thr Val Glu Thr Leu Ser Gly Gln Ala Val Val Ser Tyr
275 280 285

His Thr Val Ala Trp Ser Ser Gly Arg Gly Phe Asn Ala Thr Tyr His

290 295 300

Val Arg Gly Tyr Cys Leu Pro Trp Asp Arg Pro Cys Gly Leu Gly Ser
305 310 315 320

Gly Leu Gly Ala Ser Glu Asn Leu Gly Glu Arg Cys Tyr Ser Glu Ala
325 330 335

Gln Arg Cys Asp Gly Ser Trp Asp Cys Ala Asp Gly Thr Asp Glu Glu
340 345 350

Gly Cys Pro Gly Cys Pro Pro Gly His Phe Pro Cys Gly Ala Ala Gly
355 360 365

Thr Pro Gly Ala Thr Ala Cys Tyr Leu Pro Ala Asp Arg Cys Asn Tyr
370 375 380

Gln Thr Phe Cys Ala Asp Gly Ala Asp Glu Arg Arg Cys Arg His Cys
385 390 395 400

Gln Pro Gly Asn Phe Arg Cys Arg Asp Glu Lys Cys Val Tyr Glu Thr
405 410 415

Trp Val Cys Asp Gly Gln Pro Asp Cys Thr Asp Gly Ser Asp Glu Trp
420 425 430

Asp Cys Ser Tyr Ala Leu Pro Arg Lys Val Ile Thr Ala Ala Val Ile
435 440 445

Gly Ser Leu Val Cys Gly Leu Leu Leu Val Ile Ala Leu Gly Cys Thr
450 455 460

Cys Lys Leu Tyr Ala Ile Arg Thr Gln Glu Tyr Ser Ile Phe Ala Pro
465 470 475 480

Leu Ser Arg Met Glu Ala Glu Ile Val Gln Gln Gln Ala Pro Pro Ser
485 490 495

Tyr Gly Gln Leu Ile Ala Gln Gly Ala Ile Pro Pro Val Glu Asp Phe
500 505 510

Pro Thr Glu Asn Pro Asn Asp Asn Ser Val Leu Gly Asn Leu Arg Ser
515 520 525

Leu Leu Gln Ile Leu Arg Gln Asp Met Thr Pro Gly Gly Thr Ser Gly
530 535 540

Gly Arg Arg Arg Gln Arg Gly Arg Ser Ile Arg Arg Leu Val Arg Arg
545 550 555 560

Leu Arg Arg Trp Gly Leu Leu Pro Arg Thr Asn Thr Pro Ala Arg Ala

565 570 575

Pro Glu Thr Arg Ser Gln Val Thr Pro Ser Val Pro Ser Glu Ala Leu
580 585 590

Asp Asp Ser Thr Gly Gln Ala Cys Glu Gly Gly Ala Val Gly Gly Gln
595 600 605

Asp Gly Glu Gln Ala Pro Pro Leu Pro Ile Lys Thr Pro Ile Pro Thr
610 615 620

Pro Ser Thr Leu Pro Ala Leu Ala Thr Val Ser Glu Pro Pro Gly Pro
625 630 635 640

Leu Pro Ser Val Pro Val Glu Ser Ser Leu Leu Ser Gly Val Val Gln
645 650 655

Val Leu Arg Gly Arg Leu Leu Pro Ser Leu Trp Ser Pro Gly Pro Thr
660 665 670

Trp Thr Gln Thr Gly Thr His Thr Thr Val Leu Ser Pro Glu Asp Glu
675 680 685

Asp Asp Val Leu Leu Leu Pro Leu Ala Glu Pro Glu Val Trp Val Val
690 695 700

Glu Ala Glu Asp Glu Pro Leu Leu Ala
705 710

<210> 89
<211> 2214
<212> PRT
<213> HOMO SAPIENS

<400> 89

Met Ala Thr Arg Ser Ser Arg Arg Glu Ser Arg Leu Pro Phe Leu Phe
1 5 10 15

Thr Leu Val Ala Leu Leu Pro Pro Gly Ala Leu Cys Glu Val Trp Thr
20 25 30

Gln Arg Leu His Gly Gly Ser Ala Pro Leu Pro Gln Asp Arg Gly Phe
35 40 45

Leu Val Val Gln Gly Asp Pro Arg Glu Leu Arg Leu Trp Ala Arg Gly
50 55 60

Asp Ala Arg Gly Ala Ser Arg Ala Asp Glu Lys Pro Leu Arg Arg Lys
65 70 75 80

Arg Ser Ala Ala Leu Gln Pro Glu Pro Ile Lys Val Tyr Gly Gln Val
85 90 95

Ser Leu Asn Asp Ser His Asn Gln Met Val Val His Trp Ala Gly Glu
100 105 110

Lys Ser Asn Val Ile Val Ala Leu Ala Arg Asp Ser Leu Ala Leu Ala
115 120 125

Arg Pro Lys Ser Ser Asp Val Tyr Val Ser Tyr Asp Tyr Gly Lys Ser
130 135 140

Phe Lys Lys Ile Ser Asp Lys Leu Asn Phe Gly Leu Gly Asn Arg Ser
145 150 155 160

Glu Ala Val Ile Ala Gln Phe Tyr His Ser Pro Ala Asp Asn Lys Arg
165 170 175

Tyr Ile Phe Ala Asp Ala Tyr Ala Gln Tyr Leu Trp Ile Thr Phe Asp
180 185 190

Phe Cys Asn Thr Leu Gln Gly Phe Ser Ile Pro Phe Arg Ala Ala Asp
195 200 205

Leu Leu Leu His Ser Lys Ala Ser Asn Leu Leu Leu Gly Phe Asp Arg
210 215 220

Ser His Pro Asn Lys Gln Leu Trp Lys Ser Asp Asp Phe Gly Gln Thr
225 230 235 240

Trp Ile Met Ile Gln Glu His Val Lys Ser Phe Ser Trp Gly Ile Asp
245 250 255

Pro Tyr Asp Lys Pro Asn Thr Ile Tyr Ile Glu Arg His Glu Pro Ser
260 265 270

Gly Tyr Ser Thr Val Phe Arg Ser Thr Asp Phe Phe Gln Ser Arg Glu
275 280 285

Asn Gln Glu Val Ile Leu Glu Glu Val Arg Asp Phe Gln Leu Arg Asp
290 295 300

Lys Tyr Met Phe Ala Thr Lys Val Val His Leu Leu Gly Ser Glu Gln
305 310 315 320

Gln Ser Ser Val Gln Leu Trp Val Ser Phe Gly Arg Lys Pro Met Arg
325 330 335

Ala Ala Gln Phe Val Thr Arg His Pro Ile Asn Glu Tyr Tyr Ile Ala
340 345 350

Asp Ala Ser Glu Asp Gln Val Phe Val Cys Val Ser His Ser Asn Asn
355 360 365

Arg Thr Asn Leu Tyr Ile Ser Glu Ala Glu Gly Leu Lys Phe Ser Leu
370 375 380

Ser Leu Glu Asn Val Leu Tyr Tyr Ser Pro Gly Gly Ala Gly Ser Asp
385 390 395 400

Thr Leu Val Arg Tyr Phe Ala Asn Glu Pro Phe Ala Asp Phe His Arg
405 410 415

Val Glu Gly Leu Gln Gly Val Tyr Ile Ala Thr Leu Ile Asn Gly Ser
420 425 430

Met Asn Glu Glu Asn Met Arg Ser Val Ile Thr Phe Asp Lys Gly Gly
435 440 445

Thr Trp Glu Phe Leu Gln Ala Pro Ala Phe Thr Gly Tyr Gly Glu Lys
450 455 460

Ile Asn Cys Glu Leu Ser Gln Gly Cys Ser Leu His Leu Ala Gln Arg
465 470 475 480

Leu Ser Gln Leu Leu Asn Leu Gln Leu Arg Arg Met Pro Ile Leu Ser
485 490 495

Lys Glu Ser Ala Pro Gly Leu Ile Ile Ala Thr Gly Ser Val Gly Lys
500 505 510

Asn Leu Ala Ser Lys Thr Asn Val Tyr Ile Ser Ser Ser Ala Gly Ala
515 520 525

Arg Trp Arg Glu Ala Leu Pro Gly Pro His Tyr Tyr Thr Trp Gly Asp
530 535 540

His Gly Gly Ile Ile Thr Ala Ile Ala Gln Gly Met Glu Thr Asn Glu
545 550 555 560

Leu Lys Tyr Ser Thr Asn Glu Gly Glu Thr Trp Lys Thr Phe Ile Phe
565 570 575

Ser Glu Lys Pro Val Phe Val Tyr Gly Leu Leu Thr Glu Pro Gly Glu
580 585 590

Lys Ser Thr Val Phe Thr Ile Phe Gly Ser Asn Lys Glu Asn Val His
595 600 605

Ser Trp Leu Ile Leu Gln Val Asn Ala Thr Asp Ala Leu Gly Val Pro
610 615 620

Cys Thr Glu Asn Asp Tyr Lys Leu Trp Ser Pro Ser Asp Glu Arg Gly
625 630 635 640

Asn Glu Cys Leu Leu Gly His Lys Thr Val Phe Lys Arg Arg Thr Pro
645 650 655

His Ala Thr Cys Phe Asn Gly Glu Asp Phe Asp Arg Pro Val Val Val
660 665 670

Ser Asn Cys Ser Cys Thr Arg Glu Asp Tyr Glu Cys Asp Phe Gly Phe
675 680 685

Lys Met Ser Glu Asp Leu Ser Leu Glu Val Cys Val Pro Asp Pro Glu
690 695 700

Phe Ser Gly Lys Ser Tyr Ser Pro Pro Val Pro Cys Pro Val Gly Ser
705 710 715 720

Thr Tyr Arg Arg Thr Arg Gly Tyr Arg Lys Ile Ser Gly Asp Thr Cys
725 730 735

Ser Gly Gly Asp Val Glu Ala Arg Leu Glu Gly Glu Leu Val Pro Cys
740 745 750

Pro Leu Ala Glu Glu Asn Glu Phe Ile Leu Tyr Ala Val Arg Lys Ser
755 760 765

Ile Tyr Arg Tyr Asp Leu Ala Ser Gly Ala Thr Glu Gln Leu Pro Leu
770 775 780

Thr Gly Leu Arg Ala Ala Val Ala Leu Asp Phe Asp Tyr Glu His Asn
785 790 795 800

Cys Leu Tyr Trp Ser Asp Leu Ala Leu Asp Val Ile Gln Arg Leu Cys
805 810 815

Leu Asn Gly Ser Thr Gly Gln Glu Val Ile Ile Asn Ser Gly Leu Glu
820 825 830

Thr Val Glu Ala Leu Ala Phe Glu Pro Leu Ser Gln Leu Leu Tyr Trp
835 840 845

Val Asp Ala Gly Phe Lys Lys Ile Glu Val Ala Asn Pro Asp Gly Asp
850 855 860

Phe Arg Leu Thr Ile Val Asn Ser Ser Val Leu Asp Arg Pro Arg Ala
865 870 875 880

Leu Val Leu Val Pro Gln Glu Gly Val Met Phe Trp Thr Asp Trp Gly
885 890 895

Asp Leu Lys Pro Gly Ile Tyr Arg Ser Asn Met Asp Gly Ser Ala Ala
900 905 910

Tyr His Leu Val Ser Glu Asp Val Lys Trp Pro Asn Gly Ile Ser Val
915 920 925

Asp Asp Gln Trp Ile Tyr Trp Thr Asp Ala Tyr Leu Glu Cys Ile Glu
930 935 940

Arg Ile Thr Phe Ser Gly Gln Gln Arg Ser Val Ile Leu Asp Asn Leu
945 950 955 960

Pro His Pro Tyr Ala Ile Ala Val Phe Lys Asn Glu Ile Tyr Trp Asp
965 970 975

Asp Trp Ser Gln Leu Ser Ile Phe Arg Ala Ser Lys Tyr Ser Gly Ser
980 985 990

Gln Met Glu Ile Leu Ala Asn Gln Leu Thr Gly Leu Met Asp Met Lys
995 1000 1005

Ile Phe Tyr Lys Gly Lys Asn Thr Gly Ser Asn Ala Cys Val Pro
1010 1015 1020

Arg Pro Cys Ser Leu Leu Cys Leu Pro Lys Ala Asn Asn Ser Arg
1025 1030 1035

Ser Cys Arg Cys Pro Glu Asp Val Ser Ser Ser Val Leu Pro Ser
1040 1045 1050

Gly Asp Leu Met Cys Asp Cys Pro Gln Gly Tyr Gln Leu Lys Asn
1055 1060 1065

Asn Thr Cys Val Lys Glu Glu Asn Thr Cys Leu Arg Asn Gln Tyr
1070 1075 1080

Arg Cys Ser Asn Gly Asn Cys Ile Asn Ser Ile Trp Trp Cys Asp
1085 1090 1095

Phe Asp Asn Asp Cys Gly Asp Met Ser Asp Glu Arg Asn Cys Pro
1100 1105 1110

Thr Thr Ile Cys Asp Leu Asp Thr Gln Phe Arg Cys Gln Glu Ser
1115 1120 1125

Gly Thr Cys Ile Pro Leu Ser Tyr Lys Cys Asp Leu Glu Asp Asp
1130 1135 1140

Cys Gly Asp Asn Ser Asp Glu Ser His Cys Glu Met His Gln Cys
1145 1150 1155

Arg Ser Asp Glu Tyr Asn Cys Ser Ser Gly Met Cys Ile Arg Ser
1160 1165 1170

Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Arg Asp Trp Ser Asp
1175 1180 1185

Glu Ala Asn Cys Thr Ala Ile Tyr His Thr Cys Glu Ala Ser Asn
1190 1195 1200

Phe Gln Cys Arg Asn Gly His Cys Ile Pro Gln Arg Trp Ala Cys
1205 1210 1215

Asp Gly Asp Thr Asp Cys Gln Asp Gly Ser Asp Glu Asp Pro Val
1220 1225 1230

Asn Cys Glu Lys Lys Cys Asn Gly Phe Arg Cys Pro Asn Gly Thr
1235 1240 1245

Cys Ile Pro Ser Ser Lys His Cys Asp Gly Leu Arg Asp Cys Ser
1250 1255 1260

Asp Gly Ser Asp Glu Gln His Cys Glu Pro Leu Cys Thr His Phe
1265 1270 1275

Met Asp Phe Val Cys Lys Asn Arg Gln Gln Cys Leu Phe His Ser
1280 1285 1290

Met Val Cys Asp Gly Ile Ile Gln Cys Arg Asp Gly Ser Asp Glu
1295 1300 1305

Asp Ala Ala Phe Ala Gly Cys Ser Gln Asp Pro Glu Phe His Lys
1310 1315 1320

Val Cys Asp Glu Phe Gly Phe Gln Cys Gln Asn Gly Val Cys Ile
1325 1330 1335

Ser Leu Ile Trp Lys Cys Asp Gly Met Asp Asp Cys Gly Asp Tyr
1340 1345 1350

Ser Asp Glu Ala Asn Cys Glu Asn Pro Thr Glu Ala Pro Asn Cys
1355 1360 1365

Ser Arg Tyr Phe Gln Phe Arg Cys Glu Asn Gly His Cys Ile Pro
1370 1375 1380

Asn Arg Trp Lys Cys Asp Arg Glu Asn Asp Cys Gly Asp Trp Ser
1385 1390 1395

Asp Glu Lys Asp Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr
1400 1405 1410

Pro Gly Pro Ser Thr Cys Leu Pro Asn Tyr Tyr Arg Cys Ser Ser
1415 1420 1425

Gly Thr Cys Val Met Asp Thr Trp Val Cys Asp Gly Tyr Arg Asp
1430 1435 1440

Cys Ala Asp Gly Ser Asp Glu Glu Ala Cys Pro Leu Leu Ala Asn
1445 1450 1455

Val Thr Ala Ala Ser Thr Pro Thr Gln Leu Gly Arg Cys Asp Arg
1460 1465 1470

Phe Glu Phe Glu Cys His Gln Pro Lys Thr Cys Ile Pro Asn Trp
1475 1480 1485

Lys Arg Cys Asp Gly His Gln Asp Cys Gln Asp Gly Arg Asp Glu
1490 1495 1500

Ala Asn Cys Pro Thr His Ser Thr Leu Thr Cys Met Ser Arg Glu
1505 1510 1515

Phe Gln Cys Glu Asp Gly Glu Ala Cys Ile Val Leu Ser Glu Arg
1520 1525 1530

Cys Asp Gly Phe Leu Asp Cys Ser Asp Glu Ser Asp Glu Lys Ala
1535 1540 1545

Cys Ser Asp Glu Leu Thr Val Tyr Lys Val Gln Asn Leu Gln Trp
1550 1555 1560

Thr Ala Asp Phe Ser Gly Asp Val Thr Leu Thr Trp Met Arg Pro
1565 1570 1575

Lys Lys Met Pro Ser Ala Ser Cys Val Tyr Asn Val Tyr Tyr Arg
1580 1585 1590

Val Val Gly Glu Ser Ile Trp Lys Thr Leu Glu Thr His Ser Asn
1595 1600 1605

Lys Thr Asn Thr Val Leu Lys Val Leu Lys Pro Asp Thr Thr Tyr
1610 1615 1620

Gln Val Lys Val Gln Val Gln Cys Leu Ser Lys Ala His Asn Thr
1625 1630 1635

Asn Asp Phe Val Thr Leu Arg Thr Pro Glu Gly Leu Pro Asp Ala
1640 1645 1650

Pro Arg Asn Leu Gln Leu Ser Leu Pro Arg Glu Ala Glu Gly Val
1655 1660 1665

Ile Val Gly His Trp Ala Pro Pro Ile His Thr His Gly Leu Ile
1670 1675 1680

Arg Glu Tyr Ile Val Glu Tyr Ser Arg Ser Gly Ser Lys Met Trp
1685 1690 1695

Ala Ser Gln Arg Ala Ala Ser Asn Phe Thr Glu Ile Lys Asn Leu
1700 1705 1710

Leu Val Asn Thr Leu Tyr Thr Val Arg Val Ala Ala Val Thr Ser
1715 1720 1725

Arg Gly Ile Gly Asn Trp Ser Asp Ser Lys Ser Ile Thr Thr Ile
1730 1735 1740

Lys Gly Lys Val Ile Pro Pro Pro Asp Ile His Ile Asp Ser Tyr
1745 1750 1755

Gly Glu Asn Tyr Leu Ser Phe Thr Leu Thr Met Glu Ser Asp Ile
1760 1765 1770

Lys Val Asn Gly Tyr Val Val Asn Leu Phe Trp Ala Phe Asp Thr
1775 1780 1785

His Lys Gln Glu Arg Arg Thr Leu Asn Phe Arg Gly Ser Ile Leu
1790 1795 1800

Ser His Lys Val Gly Asn Leu Thr Ala His Thr Ser Tyr Glu Ile
1805 1810 1815

Ser Ala Trp Ala Lys Thr Asp Leu Gly Asp Ser Pro Leu Ala Phe
1820 1825 1830

Glu His Val Met Thr Arg Gly Val Arg Pro Pro Ala Pro Ser Leu
1835 1840 1845

Lys Ala Lys Ala Ile Asn Gln Thr Ala Val Glu Cys Thr Trp Thr
1850 1855 1860

Gly Pro Arg Asn Val Val Tyr Gly Ile Phe Tyr Ala Thr Ser Phe
1865 1870 1875

Leu Asp Leu Tyr Arg Asn Pro Lys Ser Leu Thr Thr Ser Leu His
1880 1885 1890

Asn Lys Thr Val Ile Val Ser Lys Asp Glu Gln Tyr Leu Phe Leu
1895 1900 1905

Val Arg Val Val Val Pro Tyr Gln Gly Pro Ser Ser Asp Tyr Val
1910 1915 1920

Val Val Lys Met Ile Pro Asp Ser Arg Leu Pro Pro Arg His Leu
1925 1930 1935

His Val Val His Thr Gly Lys Thr Ser Val Val Ile Lys Trp Glu
1940 1945 1950

Ser Pro Tyr Asp Ser Pro Asp Gln Asp Leu Leu Tyr Ala Ile Ala
1955 1960 1965

Val Lys Asp Leu Ile Arg Lys Thr Asp Arg Ser Tyr Lys Val Lys
1970 1975 1980

Ser Arg Asn Ser Thr Val Glu Tyr Thr Leu Asn Lys Leu Glu Pro
1985 1990 1995

Gly Gly Lys Tyr His Ile Ile Val Gln Leu Gly Asn Met Ser Lys
2000 2005 2010

Asp Ser Ser Ile Lys Ile Thr Thr Val Ser Leu Ser Ala Pro Asp
2015 2020 2025

Ala Leu Lys Ile Ile Thr Glu Asn Asp His Val Leu Leu Phe Trp
2030 2035 2040

Lys Ser Leu Ala Leu Lys Glu Lys His Phe Asn Glu Ser Arg Gly
2045 2050 2055

Tyr Glu Ile His Met Phe Asp Ser Ala Met Asn Ile Thr Ala Tyr
2060 2065 2070

Leu Gly Asn Thr Thr Asp Asn Phe Phe Lys Ile Ser Asn Leu Lys
2075 2080 2085

Met Gly His Asn Tyr Thr Phe Thr Val Gln Ala Arg Cys Leu Phe
2090 2095 2100

Gly Asn Gln Ile Cys Gly Glu Pro Ala Ile Leu Leu Tyr Asp Glu
2105 2110 2115

Leu Gly Ser Gly Ala Asp Ala Ser Ala Thr Gln Ala Ala Arg Ser
2120 2125 2130

Thr Asp Val Ala Ala Val Val Val Pro Ile Leu Phe Leu Ile Leu
2135 2140 2145

Leu Ser Leu Gly Val Gly Phe Ala Ile Leu Tyr Thr Lys His Arg
2150 2155 2160

Arg Leu Gln Ser Ser Phe Thr Ala Phe Ala Asn Ser His Tyr Ser
2165 2170 2175

Ser Arg Leu Gly Ser Ala Ile Phe Ser Ser Gly Asp Asp Leu Gly
2180 2185 2190

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Glu Asp  Asp Glu Asp Ala Pro  Met Ile Thr Gly Phe  Ser Asp Asp
    2195                 2200                 2205

Val Pro  Met Val Ile Ala
    2210
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<210> 90
<211> 862
<212> PRT
<213> MOUSE

<400> 90

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Met Ser Thr Ala Asp Leu Met Arg Arg Trp Val Ile Ala Leu Leu Leu
1               5                  10                  15

Ala Ala Ala Gly Val Ala Ala Glu Asp Ser Cys Ser Arg Asn Glu Phe
            20                  25                  30

Gln Cys Arg Asp Gly Lys Cys Ile Ala Ser Lys Trp Val Cys Asp Gly
        35                  40                  45

Ser Pro Glu Cys Pro Asp Gly Ser Asp Glu Ser Pro Glu Thr Cys Met
    50                  55                  60

Ser Val Thr Cys Gln Ser Asn Gln Phe Ser Cys Gly Gly Arg Val Ser
65                  70                  75                  80

Arg Cys Ile Pro Asp Ser Trp Arg Cys Asp Gly Gln Val Asp Cys Glu
                85                  90                  95

Asn Asp Ser Asp Glu Gln Gly Cys Pro Pro Lys Thr Cys Ser Gln Asp
            100                 105                 110

Asp Phe Arg Cys Gln Asp Gly Lys Cys Ile Ser Pro Gln Phe Val Cys
        115                 120                 125

Asp Gly Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala His Cys Gln
    130                 135                 140

Ala Thr Thr Cys Gly Pro Ala His Phe Arg Cys Asn Ser Ser Ile Cys
145                 150                 155                 160

Ile Pro Ser Leu Trp Ala Cys Asp Gly Asp Val Asp Cys Val Asp Gly
                165                 170                 175

Ser Asp Glu Trp Pro Gln Asn Cys Gln Gly Arg Asp Thr Ala Ser Lys
            180                 185                 190

Gly Val Ser Ser Pro Cys Ser Ser Leu Glu Phe His Cys Gly Ser Ser
        195                 200                 205
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Glu Cys Ile His Arg Ser Trp Val Cys Asp Gly Glu Ala Asp Cys Lys
210 215 220

Asp Lys Ser Asp Glu Glu His Cys Ala Val Ala Thr Cys Arg Pro Asp
225 230 235 240

Glu Phe Gln Cys Ala Asp Gly Ser Cys Ile His Gly Ser Arg Gln Cys
245 250 255

Asp Arg Glu His Asp Cys Lys Asp Met Ser Asp Glu Leu Gly Cys Val
260 265 270

Asn Val Thr Gln Cys Asp Gly Pro Asn Lys Phe Lys Cys His Ser Gly
275 280 285

Glu Cys Ile Ser Leu Asp Lys Val Cys Asp Ser Ala Arg Asp Cys Gln
290 295 300

Asp Trp Ser Asp Glu Pro Ile Lys Glu Cys Lys Thr Asn Glu Cys Leu
305 310 315 320

Asp Asn Asn Gly Gly Cys Ser His Ile Cys Lys Asp Leu Lys Ile Gly
325 330 335

Ser Glu Cys Leu Cys Pro Ser Gly Phe Arg Leu Val Asp Leu His Arg
340 345 350

Cys Glu Asp Ile Asp Glu Cys Gln Glu Pro Asp Thr Cys Ser Gln Leu
355 360 365

Cys Val Asn Leu Glu Gly Ser Tyr Lys Cys Glu Cys Gln Ala Gly Phe
370 375 380

His Met Asp Pro His Thr Arg Val Cys Lys Ala Val Gly Ser Ile Gly
385 390 395 400

Tyr Leu Leu Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp
405 410 415

Arg Ser Glu Tyr Thr Ser Leu Leu Pro Asn Leu Lys Asn Val Val Ala
420 425 430

Leu Asp Thr Glu Val Thr Asn Asn Arg Ile Tyr Trp Ser Asp Leu Ser
435 440 445

Gln Lys Lys Ile Tyr Ser Ala Leu Met Asp Gln Ala Pro Asn Leu Ser
450 455 460

Tyr Asp Thr Ile Ile Ser Glu Asp Leu His Ala Pro Asp Gly Leu Ala
465 470 475 480

Val Asp Trp Ile His Arg Asn Ile Tyr Trp Thr Asp Ser Val Pro Gly
485 490 495

Ser Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Arg Thr Leu Phe
500 505 510

Gln Glu Ala Gly Ser Arg Pro Arg Ala Ile Val Val Asp Pro Val His
515 520 525

Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys
530 535 540

Gly Gly Leu Asn Gly Val Asp Ile His Ser Leu Val Thr Glu Asn Ile
545 550 555 560

Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Ser Ser Gly Arg Leu Tyr
565 570 575

Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly
580 585 590

Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Asn Arg Leu Ala His Pro
595 600 605

Phe Ser Leu Ala Ile Tyr Glu Asp Lys Val Tyr Trp Thr Asp Val Ile
610 615 620

Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn
625 630 635 640

Leu Val Ala Glu Asn Leu Leu Ser Pro Glu Asp Ile Val Leu Phe His
645 650 655

Lys Val Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Thr Thr Ala Leu
660 665 670

Leu Pro Asn Ser Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile
675 680 685

Gly Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu
690 695 700

Leu Ala Glu Asp Met Arg Ser Cys Leu Thr Glu Val Asp Thr Val Leu
705 710 715 720

Thr Thr Gln Gly Thr Ser Ala Val Arg Pro Val Val Thr Ala Ser Ala
725 730 735

Thr Arg Pro Pro Lys His Ser Glu Asp Leu Ser Ala Pro Ser Thr Pro
740 745 750

```
Arg Gln Pro Val Asp Thr Pro Gly Leu Ser Thr Val Ala Ser Val Thr
        755                 760                 765

Val Ser His Gln Val Gln Gly Asp Met Ala Gly Arg Gly Asn Glu Glu
    770                 775                 780

Gln Pro His Gly Val Arg Phe Leu Ser Ile Phe Phe Pro Ile Ala Leu
785                 790                 795                 800

Val Ala Leu Leu Val Leu Gly Ala Val Leu Leu Trp Arg Asn Trp Arg
                805                 810                 815

Leu Lys Asn Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr Gln Lys
            820                 825                 830

Thr Thr Glu Asp Glu Leu His Ile Cys Arg Ser Gln Asp Gly Tyr Thr
        835                 840                 845

Tyr Pro Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala
    850                 855                 860
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<210> 91
<211> 862
<212> PRT
<213> MOUSE

<400> 91

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Met Ser Thr Ala Asp Leu Met Arg Arg Trp Val Ile Ala Leu Leu Leu
1               5                   10                  15

Ala Ala Ala Gly Val Ala Ala Glu Asp Ser Cys Ser Arg Asn Glu Phe
            20                  25                  30

Gln Cys Arg Asp Gly Lys Cys Ile Ala Ser Lys Trp Val Cys Asp Gly
        35                  40                  45

Ser Pro Glu Cys Pro Asp Gly Ser Asp Glu Ser Pro Glu Thr Cys Met
    50                  55                  60

Ser Val Thr Cys Gln Ser Asn Gln Phe Ser Cys Gly Gly Arg Val Ser
65                  70                  75                  80

Arg Cys Ile Pro Asp Ser Trp Arg Cys Asp Gly Gln Val Asp Cys Glu
                85                  90                  95

Asn Asp Ser Asp Glu Gln Gly Cys Pro Pro Lys Thr Cys Ser Gln Asp
            100                 105                 110

Asp Phe Arg Cys Gln Asp Gly Lys Cys Ile Ser Pro Gln Phe Val Cys
        115                 120                 125
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Asp Gly Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala His Cys Gln
130 135 140

Ala Thr Thr Cys Gly Pro Ala His Phe Arg Cys Asn Ser Ser Ile Cys
145 150 155 160

Ile Pro Ser Leu Trp Ala Cys Asp Gly Asp Val Asp Cys Val Asp Gly
165 170 175

Ser Asp Glu Trp Pro Gln Asn Cys Gln Gly Arg Asp Thr Ala Ser Lys
180 185 190

Gly Val Ser Ser Pro Cys Ser Ser Leu Glu Phe His Cys Gly Ser Ser
195 200 205

Glu Cys Ile His Arg Ser Trp Val Cys Asp Gly Glu Ala Asp Cys Lys
210 215 220

Asp Lys Ser Asp Glu Glu His Cys Ala Val Ala Thr Cys Arg Pro Asp
225 230 235 240

Glu Phe Gln Cys Ala Asp Gly Ser Cys Ile His Gly Ser Arg Gln Cys
245 250 255

Asp Arg Glu His Asp Cys Lys Asp Met Ser Asp Glu Leu Gly Cys Val
260 265 270

Asn Val Thr Gln Cys Asp Gly Pro Asn Lys Phe Lys Cys His Ser Gly
275 280 285

Glu Cys Ile Ser Leu Asp Lys Val Cys Asp Ser Ala Arg Asp Cys Gln
290 295 300

Asp Trp Ser Asp Glu Pro Ile Lys Glu Cys Lys Thr Asn Glu Cys Leu
305 310 315 320

Asp Asn Asn Gly Gly Cys Ser His Ile Cys Lys Asp Leu Lys Ile Gly
325 330 335

Ser Glu Cys Leu Cys Pro Ser Gly Phe Arg Leu Val Asp Leu His Arg
340 345 350

Cys Glu Asp Ile Asp Glu Cys Gln Glu Pro Asp Thr Cys Ser Gln Leu
355 360 365

Cys Val Asn Leu Glu Gly Ser Tyr Lys Cys Glu Cys Gln Ala Gly Phe
370 375 380

His Met Asp Pro His Thr Arg Val Cys Lys Ala Val Gly Ser Ile Gly
385 390 395 400

Tyr Leu Leu Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp
405 410 415

Arg Ser Glu Tyr Thr Ser Leu Leu Pro Asn Leu Lys Asn Val Val Ala
420 425 430

Leu Asp Thr Glu Val Thr Asn Asn Arg Ile Tyr Trp Ser Asp Leu Ser
435 440 445

Gln Lys Lys Ile Tyr Ser Ala Leu Met Asp Gln Ala Pro Asn Leu Ser
450 455 460

Tyr Asp Thr Ile Ile Ser Glu Asp Leu His Ala Pro Asp Gly Leu Ala
465 470 475 480

Val Asp Trp Ile His Arg Asn Ile Tyr Trp Thr Asp Ser Val Pro Gly
485 490 495

Ser Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Arg Thr Leu Phe
500 505 510

Gln Glu Ala Gly Ser Arg Pro Arg Ala Ile Val Val Asp Pro Val His
515 520 525

Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys
530 535 540

Gly Gly Leu Asn Gly Val Asp Ile His Ser Leu Val Thr Glu Asn Ile
545 550 555 560

Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Ser Ser Gly Arg Leu Tyr
565 570 575

Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly
580 585 590

Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Asn Arg Leu Ala His Pro
595 600 605

Phe Ser Leu Ala Ile Tyr Glu Asp Lys Val Tyr Trp Thr Asp Val Ile
610 615 620

Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn
625 630 635 640

Leu Val Ala Glu Asn Leu Leu Ser Pro Glu Asp Ile Val Leu Phe His
645 650 655

Lys Val Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Thr Thr Ala Leu
660 665 670

Leu Pro Asn Gly Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile
675 680 685

Gly Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu
690 695 700

Leu Ala Lys Asp Met Arg Ser Cys Leu Thr Glu Val Asp Thr Val Leu
705 710 715 720

Thr Thr Gln Gly Thr Ser Ala Val Arg Pro Val Val Thr Ala Ser Ala
725 730 735

Thr Arg Pro Pro Lys His Ser Glu Asp Leu Ser Ala Pro Ser Thr Pro
740 745 750

Arg Gln Pro Val Asp Thr Pro Gly Leu Ser Thr Val Ala Ser Val Thr
755 760 765

Val Ser His Gln Val Gln Gly Asp Met Ala Gly Arg Gly Asn Glu Glu
770 775 780

Gln Pro His Gly Met Arg Phe Leu Ser Ile Phe Phe Pro Ile Ala Leu
785 790 795 800

Val Ala Leu Leu Val Leu Gly Ala Val Leu Leu Trp Arg Asn Trp Arg
805 810 815

Leu Lys Asn Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr Gln Lys
820 825 830

Thr Thr Glu Asp Glu Leu His Ile Cys Arg Ser Gln Asp Gly Tyr Thr
835 840 845

Tyr Pro Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala
850 855 860

<210> 92
<211> 864
<212> PRT
<213> MOUSE

<400> 92

Met Ser Thr Ala Asp Leu Met Arg Arg Trp Val Ile Ala Leu Leu Leu
1 5 10 15

Ala Ala Ala Gly Val Ala Val Glu Asp Ser Gly Ser Arg Asn Glu Phe
20 25 30

Gln Cys Arg Asp Gly Lys Cys Ile Ala Ser Lys Trp Val Cys Asp Gly
35 40 45

Ser Pro Glu Cys Pro Asp Gly Ser Asp Glu Ser Pro Lys Thr Cys Met

50 55 60

Ser Val Thr Cys Gln Ser Asn Gln Phe Ser Cys Gly Gly Arg Val Ser
65 70 75 80

Arg Cys Ile Pro Asp Ser Trp Arg Cys Asp Gly Gln Val Asp Cys Glu
85 90 95

Asn Asp Ser Asp Glu Gln Gly Cys Pro Pro Lys Thr Cys Ser Gln Asp
100 105 110

Asp Phe Arg Cys Gln Asp Gly Lys Cys Ile Ser Pro Gln Phe Val Cys
115 120 125

Asp Gly Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala His Cys Pro
130 135 140

Ala Thr Thr Cys Gly Pro Ala His Phe Arg Cys Lys Ser Ser Ile Cys
145 150 155 160

Ile Pro Ser Leu Trp Ala Cys Asp Gly Asp Val Asp Cys Val Asp Gly
165 170 175

Ser His Glu Trp Pro Gln Asn Cys Gln Ala Glu Asp Thr Ala Ser Lys
180 185 190

Gly Val Ser Ser Pro Cys Ser Ser Leu Glu Phe His Cys Gly Ser Ser
195 200 205

Glu Cys Ile His Arg Ser Trp Val Cys Asp Gly Glu Ala Asp Cys Lys
210 215 220

Asp Lys Ser Asp Glu Glu His Cys Ala Val Ala Thr Cys Arg Pro Asp
225 230 235 240

Glu Phe Gln Cys Ala Asp Gly Ser Cys Ile His Gly Ser Arg Gln Cys
245 250 255

Asp Arg Glu His Asp Cys Lys Asp Met Ser Asp Glu Leu Gly Cys Val
260 265 270

Asn Val Thr Gln Cys Asp Gly Pro Asn Lys Phe Lys Cys His Ser Gly
275 280 285

Glu Cys Ile Ser Leu Asp Lys Val Cys Asp Ser Ala Arg Asp Cys Gln
290 295 300

Asp Trp Ser Asp Glu Pro Ile Lys Glu Cys Lys Thr Asn Glu Cys Leu
305 310 315 320

Asp Asn Asn Gly Gly Cys Ser His Ile Cys Lys Asp Leu Lys Ile Gly

325 330 335

Ser Glu Cys Leu Cys Pro Ser Gly Phe Arg Leu Val Asp Leu His Arg
340 345 350

Cys Glu Asp Ile Asp Glu Cys Gln Glu Pro Asp Thr Cys Ser Gln Leu
355 360 365

Cys Val Asn Leu Glu Gly Ser Tyr Lys Cys Glu Cys Gln Ala Gly Phe
370 375 380

His Met Asp Pro His Thr Arg Val Cys Lys Ala Val Gly Ser Ile Gly
385 390 395 400

Tyr Leu Leu Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp
405 410 415

Arg Ser Glu Tyr Thr Ser Leu Leu Pro Asn Leu Lys Asn Val Val Ala
420 425 430

Leu Asp Thr Glu Val Thr Asn Asn Arg Ile Tyr Trp Ser Asp Leu Ser
435 440 445

Gln Lys Lys Ile Tyr Ser Ala Leu Met Asp Gln Ala Pro Asn Leu Ser
450 455 460

Tyr Asp Thr Ile Ile Ser Glu Asp Leu His Ala Pro Asp Gly Leu Ala
465 470 475 480

Val Asp Trp Ile His Arg Asn Ile Tyr Trp Thr Asp Ser Val Pro Gly
485 490 495

Ser Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Arg Thr Leu Phe
500 505 510

Gln Glu Ala Gly Ser Arg Pro Arg Ala Ile Val Val Asp Pro Val His
515 520 525

Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys
530 535 540

Gly Gly Leu Asn Gly Val Asp Ile His Ser Leu Val Thr Glu Asn Ile
545 550 555 560

Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Ser Ser Gly Arg Leu Tyr
565 570 575

Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly
580 585 590

Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Asn Arg Leu Ala His Pro

595 600 605

Phe Ser Leu Ala Ile Tyr Glu Asp Lys Val Tyr Trp Thr Asp Val Ile
610 615 620

Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn
625 630 635 640

Leu Val Ala Glu Asn Leu Leu Ser Pro Glu Asp Ile Val Leu Phe His
645 650 655

Lys Val Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Thr Thr Ala Leu
660 665 670

Leu Pro Asn Gly Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile
675 680 685

Gly Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu
690 695 700

Leu Ala Lys Asp Met Arg Ser Cys Leu Thr Glu Val Asp Thr Val Leu
705 710 715 720

Thr Thr Gln Gly Thr Ser Ala Val Arg Pro Val Val Thr Ala Ser Ala
725 730 735

Thr Arg Pro Pro Lys His Ser Glu Asp Leu Ser Ala Pro Ser Thr Pro
740 745 750

Arg Gln Pro Val Asp Thr Pro Gly Leu Ser Thr Val Ala Ser Val Thr
755 760 765

Val Ser His Gln Val Gln Gly Asp Met Ala Gly Arg Gly Asn Glu Glu
770 775 780

Gln Pro His Gly Met Arg Phe Leu Ser Ile Phe Phe Pro Ile Ala Leu
785 790 795 800

Val Ala Leu Leu Val Leu Gly Ala Val Leu Leu Trp Arg Asn Trp Arg
805 810 815

Leu Lys Asn Ile Thr Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr
820 825 830

Gln Lys Thr Thr Glu Asp Glu Leu His Ile Cys Arg Ser Gln Asp Gly
835 840 845

Tyr Thr Tyr Pro Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala
850 855 860

<210> 93

<211> 873
<212> PRT
<213> MOUSE

<400> 93

Met Gly Thr Ser Ala Arg Trp Ala Leu Trp Leu Leu Leu Ala Leu Cys
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Trp Ala Pro Arg Asp Ser Gly Ala Thr Ala Ser Gly Lys Lys Ala Lys
20 25 30

Cys Asp Ser Ser Gln Phe Gln Cys Thr Asn Gly Arg Cys Ile Thr Leu
35 40 45

Leu Trp Lys Cys Asp Gly Asp Glu Asp Cys Ala Asp Gly Ser Asp Glu
50 55 60

Lys Asn Cys Val Lys Lys Thr Cys Ala Glu Ser Asp Phe Val Cys Lys
65 70 75 80

Asn Gly Gln Cys Val Pro Asn Arg Trp Gln Cys Asp Gly Asp Pro Asp
85 90 95

Cys Glu Asp Gly Ser Asp Glu Ser Pro Glu Gln Cys His Met Arg Thr
100 105 110

Cys Arg Ile Asn Glu Ile Ser Cys Gly Ala Arg Ser Thr Gln Cys Ile
115 120 125

Pro Val Ser Trp Arg Cys Asp Gly Glu Asn Asp Cys Asp Asn Gly Glu
130 135 140

Asp Glu Glu Asn Cys Gly Asn Ile Thr Cys Ser Ala Asp Glu Phe Thr
145 150 155 160

Cys Ser Ser Gly Arg Cys Val Ser Arg Asn Phe Val Cys Asn Gly Gln
165 170 175

Asp Asp Cys Asp Asp Gly Ser Asp Glu Leu Asp Cys Ala Pro Pro Thr
180 185 190

Cys Gly Ala His Glu Phe Gln Cys Ser Thr Ser Ser Cys Ile Pro Leu
195 200 205

Ser Trp Val Cys Asp Asp Asp Ala Asp Cys Ser Asp Gln Ser Asp Glu
210 215 220

Ser Leu Glu Gln Cys Gly Arg Gln Pro Val Ile His Thr Lys Cys Pro
225 230 235 240

Thr Ser Glu Ile Gln Cys Gly Ser Gly Glu Cys Ile His Lys Lys Trp
245 250 255

Arg Cys Asp Gly Asp Pro Asp Cys Lys Asp Gly Ser Asp Glu Val Asn
260 265 270

Cys Pro Ser Arg Thr Cys Arg Pro Asp Gln Phe Glu Cys Glu Asp Gly
275 280 285

Ser Cys Ile His Gly Ser Arg Gln Ser Asn Gly Ile Arg Asp Cys Val
290 295 300

Asp Gly Ser Asp Glu Val Asn Cys Lys Asn Val Asn Gln Cys Leu Gly
305 310 315 320

Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp Met Ser Lys
325 330 335

Val Cys Asp Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp Glu Pro Leu
340 345 350

Lys Glu Cys His Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Ser
355 360 365

His Ile Cys Lys Asp Leu Val Ile Gly Tyr Glu Cys Asp Cys Ala Ala
370 375 380

Gly Phe Glu Leu Ile Asp Arg Lys Thr Cys Gly Asp Ile Asp Glu Cys
385 390 395 400

Gln Asn Pro Gly Ile Cys Ser Gln Ile Cys Ile Asn Leu Lys Gly Gly
405 410 415

Tyr Lys Cys Glu Cys Ser Arg Gly Tyr Gln Met Asp Leu Ala Thr Gly
420 425 430

Val Cys Lys Ala Val Gly Lys Glu Pro Ser Leu Ile Phe Thr Asn Arg
435 440 445

Arg Asp Ile Arg Lys Ile Gly Leu Glu Arg Lys Glu Tyr Ile Gln Leu
450 455 460

Val Glu Gln Leu Arg Asn Thr Val Ala Leu Asp Ala Asp Ile Ala Ala
465 470 475 480

Gln Lys Leu Phe Trp Ala Asp Leu Ser Gln Lys Ala Ile Phe Ser Ala
485 490 495

Ser Ile Asp Asp Lys Val Gly Arg His Phe Lys Met Ile Asp Asn Val
500 505 510

Tyr Asn Pro Ala Ala Ile Ala Val Asp Trp Val Tyr Lys Thr Ile Tyr
515 520 525

Trp Thr Asp Ala Ala Ser Lys Thr Ile Ser Val Ala Thr Leu Asp Gly
530 535 540

Ala Lys Arg Lys Phe Leu Phe Asn Ser Asp Leu Arg Glu Pro Ala Ser
545 550 555 560

Ile Ala Val Asp Pro Leu Ser Gly Phe Val Tyr Trp Ser Asp Trp Gly
565 570 575

Glu Pro Ala Lys Ile Glu Lys Ala Gly Met Asn Gly Phe Asp Arg Arg
580 585 590

Pro Leu Val Thr Glu Asp Ile Gln Trp Pro Asn Gly Ile Thr Leu Asp
595 600 605

Leu Val Lys Ser Arg Leu Tyr Trp Leu Asp Ser Lys Leu His Met Leu
610 615 620

Ser Ser Val Asp Leu Asn Gly Gln Asp Arg Arg Ile Val Leu Lys Ser
625 630 635 640

Leu Glu Phe Leu Ala His Pro Leu Ala Leu Thr Ile Phe Glu Asp Arg
645 650 655

Val Tyr Trp Ile Asp Gly Glu Asn Glu Ala Val Tyr Gly Ala Asn Lys
660 665 670

Phe Thr Gly Ser Glu Leu Ala Thr Leu Val Asn Asn Leu Asn Asp Ala
675 680 685

Gln Asp Ile Ile Val Tyr His Glu Leu Val Gln Pro Ser Gly Lys Asn
690 695 700

Trp Cys Glu Asp Asp Met Glu Asn Gly Gly Cys Glu Tyr Leu Cys Leu
705 710 715 720

Pro Ala Pro Gln Ile Asn Asp His Ser Pro Lys Tyr Thr Cys Ser Cys
725 730 735

Pro Asn Gly Tyr Asn Leu Glu Glu Asn Gly Arg Glu Cys Gln Ser Thr
740 745 750

Ser Thr Pro Val Thr Tyr Ser Glu Thr Lys Asp Ile Asn Thr Thr Asp
755 760 765

Ile Leu Arg Thr Ser Gly Leu Val Pro Gly Gly Ile Asn Val Thr Thr
770 775 780

Ala Val Ser Glu Val Ser Val Pro Pro Lys Gly Thr Ser Ala Ala Trp
785 790 795 800

Ala Ile Leu Pro Leu Leu Leu Leu Val Met Ala Ala Val Gly Gly Tyr
805 810 815

Leu Met Trp Arg Asn Trp Gln His Lys Asn Met Lys Ser Met Asn Phe
820 825 830

Asp Asn Pro Val Tyr Leu Lys Thr Thr Glu Glu Asp Leu Ser Ile Asp
835 840 845

Ile Gly Arg His Ser Ala Ser Val Gly His Thr Tyr Pro Ala Ile Ser
850 855 860

Val Val Ser Thr Asp Asp Asp Leu Ala
865 870

<210> 94
<211> 1614
<212> PRT
<213> MOUSE

<400> 94

Met Glu Thr Ala Pro Thr Arg Ala Pro Pro Pro Pro Pro Pro Leu
1 5 10 15

Leu Leu Leu Val Leu Tyr Cys Ser Leu Val Pro Ala Ala Ala Ser Pro
20 25 30

Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala Gly
35 40 45

Gly Val Lys Leu Glu Ser Thr Ile Val Ala Ser Gly Leu Glu Asp Ala
50 55 60

Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr Asp
65 70 75 80

Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly Ala
85 90 95

Ala Ala Gln Asn Ile Val Ile Ser Gly Leu Val Ser Pro Asp Gly Leu
100 105 110

Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu Thr
115 120 125

Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val Leu
130 135 140

Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro Ala
145 150 155 160

His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Ala Pro Arg Ile Glu
165 170 175

Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser Asp
180 185 190

Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys Leu
195 200 205

Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu Asp
210 215 220

Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro Phe
225 230 235 240

Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln Thr
245 250 255

Arg Ser Ile His Ala Cys Asn Lys Trp Thr Gly Glu Gln Arg Lys Glu
260 265 270

Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser Gln
275 280 285

Glu Arg Gln Pro Pro Phe His Thr Pro Cys Glu Glu Asp Asn Gly Gly
290 295 300

Cys Ser His Leu Cys Leu Leu Ser Pro Arg Glu Pro Phe Tyr Ser Cys
305 310 315 320

Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Lys Thr Cys Lys
325 330 335

Thr Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu Arg
340 345 350

Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln Val
355 360 365

Gly Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu Gly
370 375 380

Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala Tyr
385 390 395 400

Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn Asp
405 410 415

Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp Thr
420 425 430

Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr Ser
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Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile Val
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Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu Asn
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Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Arg Asp Arg His Val Leu
485 490 495

Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu Gln
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Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu Val
515 520 525

Ile Asn Ile Asp Gly Thr Lys Arg Lys Thr Leu Leu Glu Asp Lys Leu
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Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp Thr
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Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala Ser
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Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys Ala
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Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Gly Asn
595 600 605

Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro Arg Ala Thr Lys Cys
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Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys Ile
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Ile Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Thr Ile His Arg
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Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr Gly
660 665 670

Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His Ile
675 680 685

Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met Asn
690 695 700

Gly Ser Ser Val Glu His Val Ile Glu Phe Gly Leu Asp Tyr Pro Glu
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Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp Thr
725 730 735

Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg Gln
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Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu Asp
755 760 765

Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro Arg
770 775 780

Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val Asp
785 790 795 800

Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln Arg
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Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn Met
820 825 830

Leu Gly Gln Glu Arg Met Val Ile Ala Asp Asp Leu Pro Tyr Pro Phe
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Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn Leu
850 855 860

His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr Leu
865 870 875 880

Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His Ser
885 890 895

Ser Arg Gln Asp Gly Leu Asn Asp Cys Val His Ser Asn Gly Gln Cys
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Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys Ala
915 920 925

Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro Ser
930 935 940

Thr Phe Leu Leu Phe Ser Gln Lys Phe Ala Ile Ser Arg Met Ile Pro
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Asp Asp Gln Leu Ser Pro Asp Leu Val Leu Pro Leu His Gly Leu Arg
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Asn Val Lys Ala Ile Asn Tyr Asp Pro Leu Asp Lys Phe Ile Tyr Trp
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Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr Gln
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Pro Ser Met Leu Thr Ser Pro Ser Gln Ser Leu Ser Pro Asp Arg
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Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu Phe
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Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu Asp
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Leu Thr Val Leu Gly Arg His Leu Tyr Trp Ile Asp Arg Gln Gln
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Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg Thr
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Arg Val Gln Gly Arg Val Thr His Leu Thr Gly Ile His Ala Val
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Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala Arg
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Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln Asn
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Cys Asp Gly Phe Pro Glu Cys Ala Asp Gln Ser Asp Glu Glu Gly
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Cys Pro Val Cys Ser Ala Ser Gln Phe Pro Cys Ala Arg Gly Gln
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Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys Gln
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Gln Phe Arg Cys Thr Ser Gly Gln Cys Val Leu Ile Lys Gln Gln
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Cys Asp Ser Phe Pro Asp Cys Ala Asp Gly Ser Asp Glu Leu Met
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Cys Glu Ile Asn Lys Pro Pro Ser Asp Asp Ile Pro Ala His Ser
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Ser Ala Ile Gly Pro Val Ile Gly Ile Ile Leu Ser Leu Phe Val
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Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Met Cys Gln Arg
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Tyr Thr Gly Ala Ser Gly Pro Phe Pro His Glu Tyr Val Gly Gly
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Ala Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser Gln
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His Gly Pro Phe Pro Gly Ile Pro Cys Ser Lys Ser Val Met Ser
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Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser Thr
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Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser Pro
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Ala Thr Asp Pro Ser Leu Tyr Asn Val Asp Val Phe Tyr Ser Ser
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Gly Ser Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Val Ile Arg
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Asp Phe Ser Cys Gly Gly Arg Val Asn Arg Cys Ile Pro Gln Phe Trp
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Arg Cys Asp Gly Gln Val Asp Cys Asp Asn Gly Ser Asp Glu Gln Gly
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Cys Pro Pro Lys Thr Cys Ser Gln Asp Glu Phe Arg Cys His Asp Gly
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Asp Asn Asp Pro Asp Cys Glu Asp Gly Ser Asp Glu Trp Pro Gln Arg
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Cys Arg Gly Leu Tyr Val Phe Gln Gly Asp Ser Ser Pro Cys Ser Ala
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Phe Glu Phe His Cys Leu Ser Gly Glu Cys Ile His Ser Ser Trp Arg
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Cys Asp Gly Gly Pro Asp Cys Lys Asp Lys Ser Asp Glu Glu Asn Cys
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Ala Val Ala Thr Cys Arg Pro Asp Glu Phe Gln Cys Ser Asp Gly Asn
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Cys Ile His Gly Ser Arg Gln Cys Asp Arg Glu Tyr Asp Cys Lys Asp
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Met Ser Asp Glu Val Gly Cys Val Asn Val Thr Leu Cys Glu Gly Pro
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Asn Lys Phe Lys Cys His Ser Gly Glu Cys Ile Thr Leu Asp Lys Val
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Cys Asn Met Ala Arg Asp Cys Arg Asp Trp Ser Asp Glu Pro Ile Lys
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Glu Cys Gly Thr Asn Glu Cys Leu Asp Asn Asn Gly Gly Cys Ser His
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Val Cys Asn Asp Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly
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Phe Gln Leu Val Ala Gln Arg Arg Cys Glu Asp Ile Asp Glu Cys Gln
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Asp Pro Asp Thr Cys Ser Gln Leu Cys Val Asn Leu Glu Gly Gly Tyr
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Lys Cys Gln Cys Glu Glu Gly Phe Gln Leu Asp Pro His Thr Lys Ala
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Pro Asn Leu Arg Asn Val Val Ala Leu Asp Thr Glu Val Ala Ser Asn
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Arg Ile Tyr Trp Ser Asp Leu Ser Gln Arg Met Ile Cys Ser Thr Gln
            420                 425                 430

Leu Asp Arg Ala His Gly Val Ser Ser Tyr Asp Thr Val Ile Ser Arg
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Asp Ile Gln Ala Pro Asp Gly Leu Ala Val Asp Trp Ile His Ser Asn
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Ile Tyr Trp Thr Asp Ser Val Leu Gly Thr Val Ser Val Ala Asp Thr
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Lys Gly Val Lys Arg Lys Thr Leu Phe Arg Glu Asn Gly Ser Lys Pro
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Arg Ala Ile Val Val Asp Pro Val His Gly Phe Met Tyr Trp Thr Asp
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Trp Gly Thr Pro Ala Lys Ile Lys Lys Gly Gly Leu Asn Gly Val Asp
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Ile Tyr Ser Leu Val Thr Glu Asn Ile Gln Trp Pro Asn Gly Ile Thr
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Leu Asp Leu Leu Ser Gly Arg Leu Tyr Trp Val Asp Ser Lys Leu His
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Ser Ile Ser Ser Ile Asp Val Asn Gly Gly Asn Arg Lys Thr Ile Leu
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Glu Asp Glu Lys Arg Leu Ala His Pro Phe Ser Leu Ala Val Phe Glu
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Asp Lys Val Phe Trp Thr Asp Ile Ile Asn Glu Ala Ile Phe Ser Ala
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Asn Arg Leu Thr Gly Ser Asp Val Asn Leu Leu Ala Glu Asn Leu Leu
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Ser Pro Glu Asp Met Val Leu Phe His Asn Leu Thr Gln Pro Arg Gly
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Val Asn Trp Cys Glu Arg Thr Thr Leu Ser Asn Gly Gly Cys Gln Tyr
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Leu Cys Leu Pro Ala Ser Gln Ile Asn Pro His Ser Pro Lys Phe Thr
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Cys Ala Cys Pro Asp Gly Met Leu Leu Ala Arg Asp Met Arg Ser Cys
675 680 685

Leu Thr Glu Ala Glu Ala Ala Val Ala Thr Gln Glu Thr Ser Thr Val
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Arg Leu Lys Val Ser Ser Thr Ala Val Arg Thr Gln His Thr Thr Thr
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Arg Pro Val Pro Asp Thr Ser Arg Leu Pro Gly Ala Thr Pro Gly Leu
725 730 735

Thr Thr Val Glu Ile Val Thr Met Ser His Gln Ala Leu Gly Asp Val
740 745 750

Ala Gly Arg Gly Asn Glu Lys Lys Pro Ser Ser Val Arg Ala Leu Ser
755 760 765

Ile Val Leu Pro Ile Val Leu Leu Val Phe Leu Cys Leu Gly Val Phe
770 775 780

Leu Leu Trp Lys Asn Trp Arg Leu Lys Asn Ile Asn Ser Ile Asn Phe
785 790 795 800

Asp Asn Pro Val Tyr Gln Lys Thr Thr Glu Asp Glu Val His Ile Cys
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115 120 125

Gln Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln
130 135 140

Leu Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val
145 150 155 160

Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser
165 170 175

His Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His Arg
180 185 190

Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser
195 200 205

<210> 106
<211> 126
<212> PRT
<213> DANIO RERIO

<400> 106

Gly Cys Arg Glu Leu Arg Ser Thr Lys Tyr Ile Ser Asp Gly Gln Cys

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20 25 30

Pro Thr His Leu Leu Pro Asn Trp Ile Gly Gly Gly His Tyr Trp Ser
35 40 45

Arg Arg Asp Ala Gln Glu Trp Arg Cys Val Thr Asp Arg Thr Arg Thr
50 55 60

Gln Arg Ile Lys Leu Gln Cys Gln Asp Gly Thr Thr Arg Thr Tyr Lys
65 70 75 80

Ile Thr Ala Val Thr Ser Cys Thr Cys Lys Arg Tyr Thr Arg Gln Asn
85 90 95

Asn Glu Ser Ser His Ala Pro Gln Ser His Ser Lys Asp His Pro Leu
100 105 110

Gln Ser Pro Lys Lys Lys Lys Ser Lys Asn Lys Asn Ser Lys
115 120 125

<210> 107
<211> 213
<212> PRT
<213> MONKEY

<400> 107

Met Gln Leu Pro Leu Ala Leu Cys Leu Val Cys Leu Leu Val His Ala
1 5 10 15

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20 25 30

Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro Pro Pro
35 40 45

Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg
50 55 60

Pro Pro His His Pro Phe Glu Thr Lys Asp Val Ser Glu Tyr Ser Cys
65 70 75 80

Arg Glu Leu His Phe Thr Arg Tyr Val Thr Asp Gly Pro Cys Arg Ser
85 90 95

Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala
100 105 110

Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser
115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val
130 135 140

Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg Ala Arg Lys Val Arg
145 150 155 160

Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln
165 170 175

Ser Glu Leu Lys Asp Phe Gly Pro Glu Ala Ala Arg Pro Gln Lys Gly
180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu
195 200 205

Leu Glu Asn Ala Tyr
210

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<211> 618
<212> DNA
<213> DROSOPHILA

<400> 108
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cctgcgagcc cgagcagcaa cagcacgttg aaccaagcca ggaacggagg gaggcactac 180

gccggcacgg gctccgaccg taacaatcgc gttcaagttg gctgccggga actgcgatct 240

accaagtaca tctcagacgg ccagtgcacc agcatcaatc ccctgaagga gctggtgtgt 300

gctggcgaat gcctcccctt gccgctcctg cccaactgga ttggaggagg ttatggaacc 360

aagtactgga gcagacggag ctcgcaagag tggagatgtg tcaatgacaa aactcgcacc 420

cagaggatcc agctgcagtg ccaggatgga agtataagaa cctacaaaat aactgtggtc 480

acggcctgca agtgcaagcg atacaccagg cagcacaacg agtccagcca caactttgag 540

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agcaaacata gtacaagt 618

<210> 109
<211> 176
<212> PRT
<213> TAURUS

<400> 109

Asn Asp Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro
1 5 10 15

Leu Pro Glu Leu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly
20 25 30

Arg Pro Pro His His Pro Phe Glu Thr Lys Asp Ala Ser Glu Tyr Ser
35 40 45

Cys Arg Glu Leu His Phe Thr Arg Tyr Val Thr Asp Gly Pro Cys Arg
50 55 60

Ser Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro
65 70 75 80

Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro
85 90 95

Ser Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg
100 105 110

Val Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg Ala Arg Lys Val
115 120 125

Arg Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn
130 135 140

Gln Ser Glu Leu Lys Asp Phe Gly Pro Glu Ala Ala Arg Pro Gln Thr
145 150 155 160

Gly Arg Lys Leu Arg Pro Arg Ala Arg Gly Thr Lys Ala Ser Arg Ala
165 170 175

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<211> 532
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agaccaaaga cgcctccgag tacagctgcc gggagctgca cttcacccgc tacgtgaccg 180

atgggccgtg ccgcagcgcc aagccggtca ccgagctggt gtgctcgggc cagtgcggcc 240

cggcgcgcct gctgcccaac gccatcggcc gcggcaagtg gtggcgccca agcgggcccg 300

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<211> 1581
<212> DNA
<213> RABBIT

<400> 113
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<210> 114
<211> 56
<212> PRT
<213> MOUSE

<220>
<221> misc_feature
<222> (22)..(22)
<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

<400> 114

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Thr Ser Ile Ser Pro Xaa Lys Glu Leu Val Cys Ala Gly Glu Cys Leu
20 25 30

Pro Leu Pro Val Leu Pro Asn Trp Ile Gly Gly Gly Tyr Gly Thr Lys
35 40 45

Tyr Trp Ser Arg Arg Ser Xaa Gln
50 55

<210> 115
<211> 77
<212> PRT
<213> MOUSE

<400> 115

Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln Leu
1 5 10 15

Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val Thr

20 25 30

Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser His
35 40 45

Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His Arg Glu
50 55 60

Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser
65 70 75

<210> 116
<211> 31
<212> PRT
<213> MOUSE

<220>
<221> misc_feature
<222> (22)..(22)
<223> Xaa can be any naturally occurring amino acid

<400> 116

Gly Cys Arg Glu Leu Arg Ser Thr Lys Tyr Ile Ser Asp Gly Gln Cys
1 5 10 15

Thr Ser Ile Ser Pro Xaa Lys Glu Leu Val Cys Ala Gly Glu Cys
20 25 30

<210> 117
<211> 28
<212> PRT
<213> MOUSE

<220>
<221> misc_feature
<222> (24)..(24)
<223> Xaa can be any naturally occurring amino acid

<400> 117

Leu Pro Leu Pro Val Leu Pro Asn Trp Ile Gly Gly Gly Tyr Gly Thr
1 5 10 15

Lys Tyr Trp Ser Arg Arg Ser Xaa Gln Glu Trp Arg
20 25

<210> 118
<211> 43
<212> PRT
<213> MOUSE

<400> 118

Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln Leu Gln Cys Gln
1 5 10 15

Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val Thr Ala Cys Lys
20 25 30

Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser
35 40

<210> 119
<211> 31
<212> PRT
<213> MOUSE

<400> 119

Ser His Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His
1 5 10 15

Arg Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser
20 25 30

<210> 120
<211> 52
<212> PRT
<213> MOUSE

<400> 120

Ser Cys Arg Glu Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys
1 5 10 15

Arg Ser Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly
20 25 30

Pro Ala Arg Leu Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg
35 40 45

Pro Asn Gly Pro
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<210> 121
<211> 83
<212> PRT
<213> MOUSE

<400> 121

Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu
1 5 10 15

Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val
20 25 30

Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu
35 40 45

Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys
50 55 60

Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu Glu
65 70 75 80

Asn Ala Tyr

<210> 122
<211> 31
<212> PRT
<213> MOUSE

<400> 122

Ser Cys Arg Glu Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys
1 5 10 15

Arg Ser Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys
20 25 30

<210> 123
<211> 24
<212> PRT
<213> MOUSE

<400> 123

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1 5 10 15

Arg Pro Asn Gly Pro Asp Phe Arg
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<210> 124
<211> 44
<212> PRT
<213> MOUSE

<400> 124

Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu Leu Cys Pro
1 5 10 15

Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val Ala Ser Cys
20 25 30

Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser
35 40

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<211> 36
<212> PRT
<213> MOUSE

<400> 125

Glu Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg
1 5 10 15

Lys Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu
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Glu Asn Ala Tyr
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ccggcacacc ccagcagcaa cagcaccctg aatcaagcca ggaatggagg caggcatttc 180

agtagcactg gactggatcg aaacagtcga gttcaagtgg gctgcaggga actgcggtcc 240

accaaataca tttcggacgg ccagtgcacc agcatcagcc ctntgaagga gctggtgtgc 300

gcgggcgagt gcttgcccct gccggtgctt cccaactgga tcggaggagg ctatggaaca 360

aagtactgga gccggaggag ctntcaggag tggcggtgtg tcaacgacaa gacgcgcacc 420

cagaggatcc agctgcagtg tcaggacggc agcacgcgca cctacaaaat caccgtggtc 480

acggcgtgca agtgcaagag gtacacccgt cagcacaacg agtccagcca caactttgaa 540

agcgtgtcgc ccgccaagcc cgcccagcac cacagagagc ggaagagagc cagcaaatcc 600

agcaagcaca gtctgagc 618

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<400> 127
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tgtttggctt ttaaaaatga tgccacagaa atcctttatt cacatgtggt taaacctgtc 120

ccggcacacc ccagcagcaa cagcaccctg aatcaagcca ggaatggagg caggcatttc 180

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<223> n is a, c, g, or t

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aactggatcg gaggaggcta tggaacaaag tactggagcc ggaggagctn tcaggagtgg 180

cggtgtgtca acgacaagac gcgcacccag aggatccagc tgcagtgtca ggacggcagc 240

acgcgcacct acaaaatcac cgtggtcacg gcgtgcaagt gcaagaggta cacccgtcag 300

cacaacgagt ccagccacaa ctttgaaagc gtgtcgcccg ccaagcccgc ccagcaccac 360

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<213> XENOPUS

<400> 131
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<210> 132
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atcctgatga aaaactgttt ggcttttaaa aatgatgcca cagaaatcct ttattcacat 180

gtggttaaac ctgtttcagc acaccccagc agcaacagca ccttgaatca agccaggaat 240

ggaggcaggc acttcagtag cacgggactg gatcgaaata gtcgagttca agtgggctgc 300

agggaactgc ggtccaccaa atacatctcg gatggccagt gcaccagcat cagccctctg 360

aaggagctgg tgtgcgcggg tgagtgcttg cccttgccag tgcttcccaa ctggatcgga 420

ggaggctacg gaacaaagta ctggagccgg aggagctccc aggagtggcg gtgtgtcaac 480

gacaagacgc gcacccagag aatccagctg cagtgtcagg acggcagcac acgcacctac 540

aaaatcaccg tggtcacagc gtgcaagtgc aagaggtaca cccggcagca caacgagtcc 600

agccacaact ttgaaagcgt gtctcccgcc aagctcgccc agcaccacag agagcggaag 660

agagccagca aatccagcaa gcacagtctg agctagagct ggactgacta gaaagcatct 720

gctccccaga tttgattgcg tggaagactc gctcgagcct gccattgctc ttttctcact 780

tgaaagtata tgctttctgc tttgatcagg cccagcaggc tgtccttctc tgggaccttc 840

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gccaggcatc ccatagtttc acccctccc ccagtcattt ctttcaaaag cacctgatgc 960

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actaaatccc tccgaaccgg agaagttcaa tcaaaaaaaa aaatgtatct tcacagaaca 1080

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gcaatgcaag gcagcagcta ataggtaaag ccggttattt atttgtcgat gttgttattt 1320

aatgagctcg cgcatgtgat tttttttcca aatgttaatt tttttttata ttttgaagct 1380

ttttcatgta cctaaatatt tcccaatacg atttgtggtt ggtctagaaa tatgaaaata 1440

catgttgtag atatgtaaaa ataaatattt tagactcctt atatattaca cggttcctca 1500

tacactttgt cattagcgtg gttccctgta aagctgaagt tatgtaatac tttattattt 1560

agtccatgaa atcagaaggc agcttgacct tcggtgccat cggtttcttt taataaacat 1620

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aacctttatc gtcgacgagc aattgg 26

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<210> 139
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<400> 139
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<210> 140
<211> 35
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<400> 140
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